SELECTED DERIVATIVES OF 3,7-DIHETERABICYCLO[3.3.1]-NONANES WHICH POSSESS MULTI-CLASS ANTIARRHYTHMIC ACTIVITY

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CHAPTER I

HISTORICAL

Introduction

One of the most traumatic personal medical problem is the phenomenon of sudden cardiac death (SCD).[51] An individual's heart can cease to function, most often when the person appears to be in good health, and prompt SCD can occur without warning. The victim often experiences shortness of breath, sweating, and fatigue. When the heart stops pumping, blood flow diminishes to the brain and consciousness is lost within seconds. Gasping for air and seizures follow as death rapidly approaches.[21]

The term 'sudden cardiac death' implies that breathing and the circulation of blood has stopped. This is usually caused from underlying heart desease such as atherosclerosis of the coronary arteries.[21] Each year in the United States, more than 500,000 deaths occur in the adult population which are caused from the SCD syndrome.[51] More than 80% of these deaths are due to ventricular fibrillation (VF; chaotic contraction of the heart with minimum pumping action) which is usually followed by ventricular arrhythmias.[36] The mechanism which triggers VF is unclear. Several suggested causes for this effect are: 1) myocardial ischemia (resulting from reduced blood flow to the heart muscle), 2) electrolytic imbalance, 3) platelet abnormalities in the blood, and 4) psychological stress.[21]

Patients suffering from post-myocardial infarction usually experience ventricular tachycardia [VT; irregular beating pattern with an elevated heart rate and with blood flow reduced significantly).[39] Today, there are a limited number of agents available for the treatment of lethal VT. Antiarrhythmic agents (AAA) seem to be effective in a number

of patients, but the efficacy of the agent depends greatly on the nature of the individual VT.

Vaughan Williams Classification

Physicians have difficulties in prescribing antiarrhythmic agents (AAA) to patients due to the many different symptoms observed. It might be mistakenly concluded that drugs within a particular classification are clinically similar and, if patients fail to respond to a drug in a given class, they would not respond to the others in that class. The Vaughan Williams[83] approach to classify AAA was intended to be a classification of antiarrhythmic "actions" not of "drugs" The current classification is broken down into 5 modes of action, with class I subdivided into three different categories. Table I illustrates the first four different class actions and gives a few prototypes which fit into each specific

TABLE I[a]

VAUGHAN WILLIAMS CLASSIFICATION

Class	Action	Prototypes
I	Sodium channel blockade	Lidocaine Procainamide
II	Antagonism of sympathetic nervous system	Propranolol
III	Increased refractoriness	Sotalol Amiodarone
IV	Calcium channel blockade	Tedisamil Verapamil

[a]Reference 83.

group. Class I AAA, such as lidocaine, block the sodium channel during the repolarization of the heart cells, which results in slowing of the conduction. The phase 0 upstroke of the action potential in the electrocardiograph (ECG; Figure 1) is regulated by the sodium influx (via sodium channels) across the cell membrane. Antagonism of the sympathetic nervous system (i.e., propranolol) results in reduction of the heart rate and are class II agents. Amiodarone is categorized as having class III action which increases refractoriness [prolongation of the action potential duration (APD)]. There is much evidence to indicate that a shortened APD is a significant factor in explaining high incidence of atrial fibrillation (AF).[27]

Originally, class I AAA were believed to have very similar actions but this was found untrue with most of the existing drugs. Although these agents differed in many activities, they all have one common property, that is "interferring specifically with the process by which depolarizing charge is transferred across the membrane (i.e., by fast inward depolarizing current carried by sodium ions)".[79] Significant differences in action among the class I agents caused Vaughan Williams to subdivided these drugs into class Ia, Ib, and Ic.

This subclassification (Table II) was based on the effects each agent exerted on the following parameters: 1) QRS complex[14] of the electrocardiogram (Figure 1) is the point at which heart cells undergo depolarization. Two major electrical processes consisting of depolarization (activation) and repolarization (recovery) occur during muscular activity. QRS complex is defined as the time alloted for an polarized cell to become fully depolarized in which a sudden loss of semipermeability of the membrane around the cell so that there is a flow of ions across the cell; 2) Conduction of the heart is controlled by the ability of an agents to block sodium channels across the cell membrane; 3) Effective Refractory Period (ERP)[14] is the time elapsed for the QRS complex of the electrocardiogram; and 4) APD or the QT interval is the time the cell is allowed to depolarize and repolarize. When the QT interval is shortened significantly, the patients

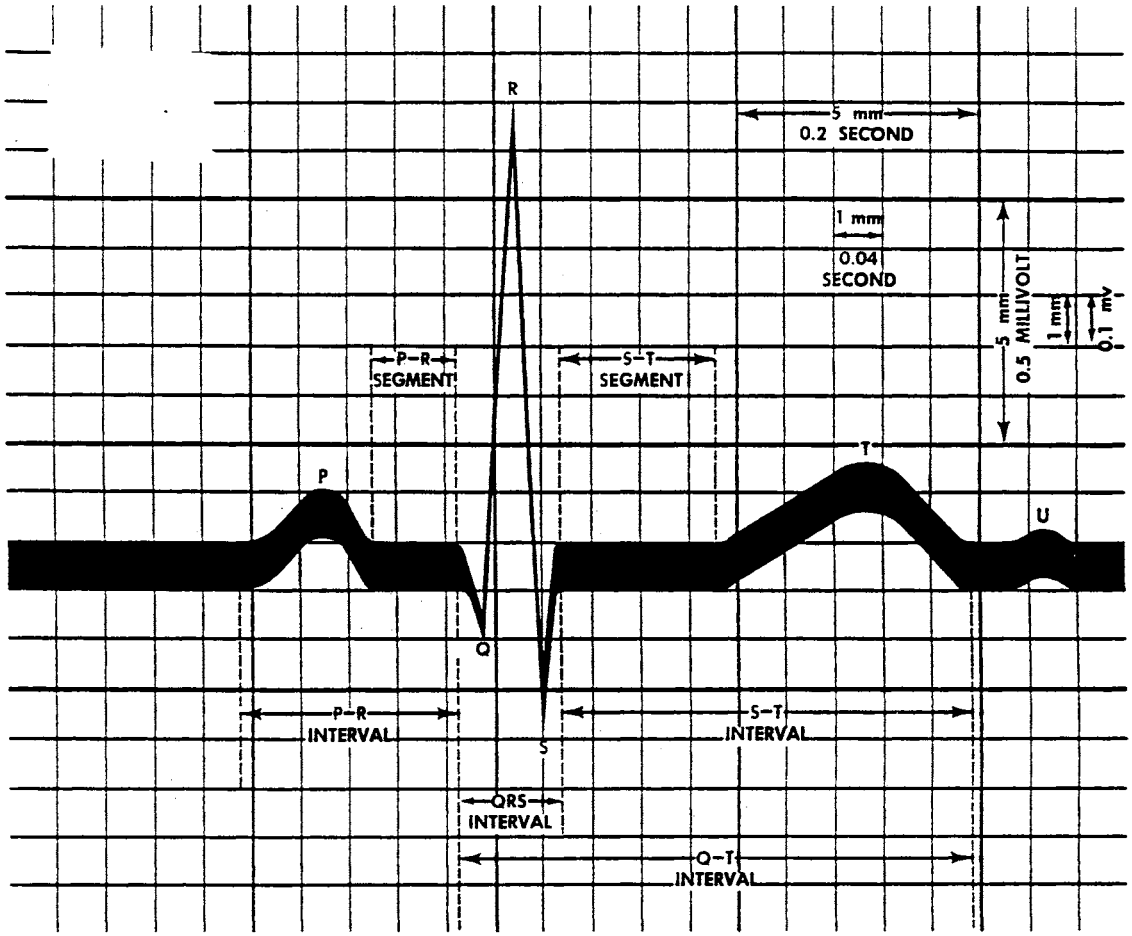


Figure 1. Illustration of an Electrocardiogram (ECG) Output

TABLE II[a]

CLINICAL SUBDIVISIONS OF CLASS I ANTIARRHYTHMIC DRUGS

Effect on:	Group A	B	C
	Quinidine Procainamide Disopyramide	Lidocaine Mexiletine Tocainide	Lorcainide Encainide Flecainide
1. QRS[b]	widen at high concentration	none in sinus rhythm	widen at low concentrations
2. Conduction	slowed at high concentrations	none in sinus rhythm	slowed at low concentrations
3. ERP[c]	lengthened absolutely and relative to APD	lengthened in relation to APD	very little change
4. Action Potential Duration	lengthened at high concentration	shortened	very little change

[a] Reference 83.
[b]QRS refers to the QRS interval of the electrocardiograph.
[c]ERP refers to effective refractory period of the ECG.

most often experience reentry.[14] For example, when an impulse in the cardiac conduction system is slowed due to failure to pass an ischemic area, the result is a premature contraction. This premature contraction can initiate atrial flutter or fibrillation.[11,52]

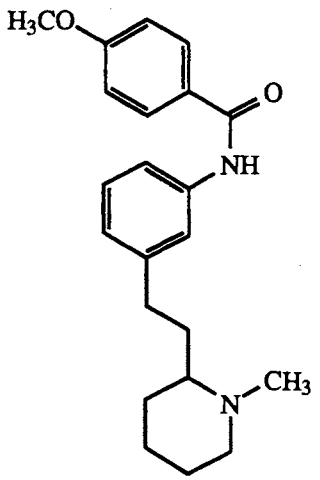
The most important limitation to the current theory is the fact that many of the currently available drugs possess multiple class activity.[1] Clinical studies have revealed that certain individuals have approximately an equal chance of responding to any agent, independent of their response to other drugs of one class.[86] Actions of AAA might be anticipated with a full understanding of the multiple actions of the agents and their metabolites, combined with knowledge of their clinical pharmacology so that one might predict the factors influencing drug action.[1,86]

There are a variety of clinical agents available for the management of heart arrhythmias. The following guidelines are the general basis for an agent's use: (1) knowledge of the electrophysiological mechanism, (2) knowledge of the electropharmacological properties of the agent and (3) an understanding of the pharmacokinetics. One of the most adverse side effects is the conversion of nonsustained VT (NSVT) to sustained ventricular tachycardia (SVT). Thus, the selection of the agent to eliminate the SVT can be critical or sudden death may result.[39]

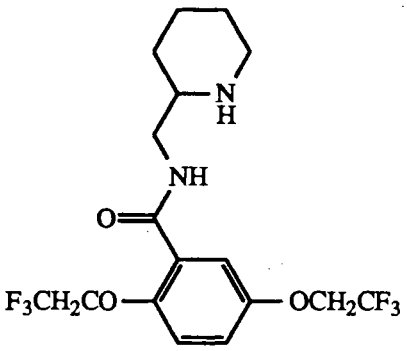
The CAST Study

Until the mid 1980's, class I antiarrhythmic agents were the drugs of choice in the treatment of VT since most of the available clinical agents fell within this classification. The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test antiarrhythmic drug therapy in the suppression of asymptomatic or mild symptomatic ventricular arrhythmias after myocardial infarction to determine if there occurred a reduction in the rate of death from arrhythmias.[63] Preliminary results of the CAST study were made public in 1989, and these findings changed the therapy of arrhythmias and directed researchers to new areas not previously explored.

Prior to the CAST study, results from the Cardiac Arrhythmia Pilot Study (CAPS)[81] showed that encainide (**1**), and flecainide (**2**) suppressed arrhythmias in the targeted population of their experiments. Thus, these two drugs were selected for the more



Encainide
1



Flecainide
2

sophisticated CAST study. Initial trials were to identify patients that would respond to treatment with one of the drugs. Those who responded were then randomly assigned to receive either the therapy with the agent or with a placebo. The experiment comprised of 2309 patients in which only 1727 showed suppression of their arrhythmias. Those patients were then assigned the blind therapy: 1455 were asigned to encainide, flecainide, or placebo, and 272 were assigned to moricizine.[64]

Surprisingly, the rate of death from arrhythmias in the group with the placebo was lower than the group receiving encainide and flecainide. Table III shows the number of deaths caused by arrhythmias and a nonarrhythmic cardiac event.[63] The adverse outcome in the patients could have reflected proarrhythmic properties of the two agents.[35,50] Both agents were found to slow myocardial conduction velocity profoundly, an effect that might facilitate reentry.[78] Reentry is defined as any irregular impulse in the heart cells which can cause ventricular tachycardias to reoccur.[14] One other possible explanation

for these results is that active metabolites of encainide could be eliminated slowly and thus accumulate and facilitate proarrhythmic effects.[87] However, flecainide (**2**) is not known to form active metabolites.[87] The majority of the deaths not due to arrhythmias

TABLE III[a]

EVENTS IN 1455 PATIENTS RANDOMLY ASSIGNED TO RECEIVE ENCAINIDE (1), FLECAINIDE (2), OR MATCHING PLACEBO

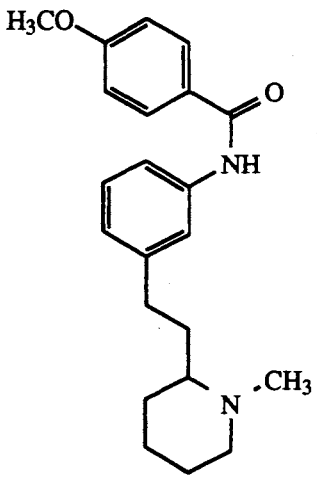
Variable	Encainide/ Flecainide (N = 730)	Placebo (N = 725)
Average exposure (days)	293	300
Death from arrhythmia or cardiac arrest	33	9
Other cardiac death	14	6
Noncardiac or unclassified death or cardiac arrest	9	7
Total deaths or cardiac arrests	56	22

[a]References 63, 64.

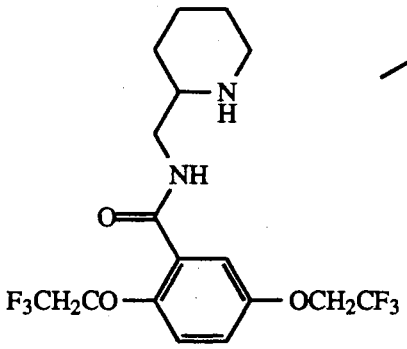
were attributed to acute myocardial ischemia.[63,64] Most physicians now believe that more of the clinically available agents should be subjected to the same kinds of studies.

Class I Antiarrhythmic Agents

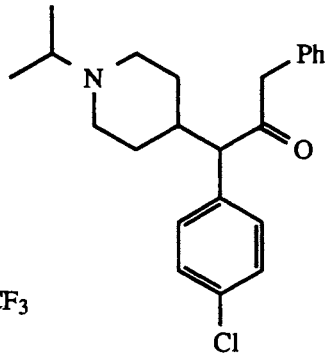
Currently, the majority of the prescribed clinical AAA possess class I activity. Some examples include encainide (**1**), flecainide (**2**), lorcainide (**3**), quinidine (**4**), procainamide (**5**), disopyramide (**6**), lidocaine (**7**), tocainide (**8**), and mexiletine (**9**). These agents have



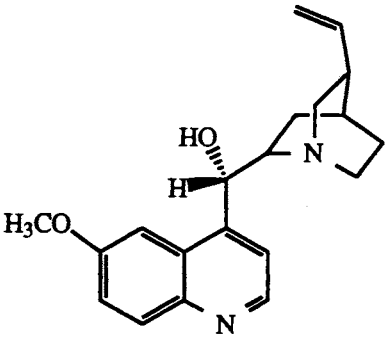
1 (Encainide)



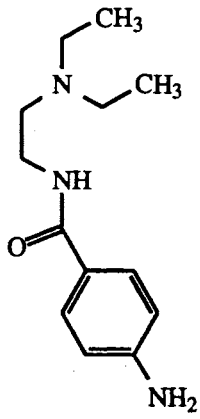
2 (Flecainide)



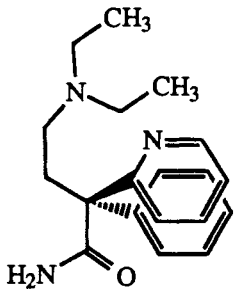
3 (Lorcainide)



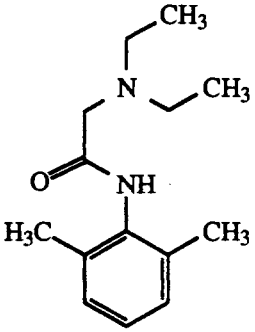
4 (Quinidine)



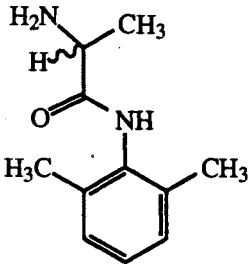
5 (Procainamide)



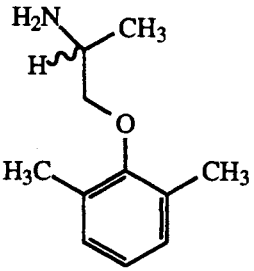
6 (Disopyramide)



7 (Lidocaine)



8 (Tocainide)



9 (Mexiletine)

been found to be the most useful in the treatment of VT.[39] Pharmacology and clinical experiences have been extensively reviewed on these class I antiarrhythmic agents.[11,15,39,41,46,52] Along with abolishing or reducing the rate of VT, these agents also have some other physiological features of interest.

Quinidine (**4**) is a class Ia antiarrhythmic drug and has been the prototype of local anesthetic antiarrhythmic compounds. Reduction of V_{max} (dV/dt_{max} or maximum rate of depolarization)[11] is effected by the blocking of the activated sodium channel. This drug also prolongs the APD and produces a marked prolongation of atrial refractoriness with ventricular refractoriness being much less effected. This effect of quinidine has been explained by a decrease in potassium outward current.[11,41]

Procainamide (**5**) has been a widely used class Ia antiarrhythmic agent which is popular because of easy administration, clinical efficacy, and patients tolerance. This drug has electrophysiological properties similar to those of quinidine in that it induces rate-dependent depression of V_{max} and, therefore, needs more time to reach a steady state V_{max} as compared to lidocaine.[11,39,41]

Disopyramide (**6**) is a class Ia agent and shares many electrophysiological and pharmacological properties wtih quinidine and procainamide. It prevents induction of VT in about one third of patients but tolerance is limited primarily by anticholinergic side effects such as dry eyes and mouth and retention of urine. Limited use is also seen in patients with impaired left ventricular functions.[42]

Lidocaine (**7**) was originally developed as a local anesthetic and is still widely used for this purpose today. Arrhythmias are related to disturbances in the membrane ion potentials, and it is not surprising that local anesthetics have antiarrhythmic activity. After more than 25 years of clinical use, lidocaine is still considered to be the most effective agent against ventricular arrhythmias and has been termed as "the gold standard" by which all other antiarrhythmic drugs should be judged.[11] Lidocaine (**7**) is a prototype of class Ib agents in which it shortens the APD and refractoriness but prolongs

the recovery of exciteability relative to the change in repolarization.[42] It differs from quinidine by having only a small effect on V_{max} of normal cardiac fibers but markedly depresses V_{max} in partially depolarized fibers as might result from myocardial ischemia.[42,46]

Tocainide (**8**), a class Ib agent, has electrophysiological and hemodynamic effects similar to those of lidocaine (**7**). This drug has one advantage over lidocaine in that it possesses a high oral bioavailabilty with a mean half-life of 11 hours in humans. Effectiveness in the treatment of ventricular arrhythmias and ineffective against atrial arrhythmias are the same results experienced from lidocaine.[11,46]

Mexiletine (**9**) has been marketed in parts of Europe since 1976 and belongs to the family of local anesthetics which also function as antiarrhythmic agents. It has electrophysiological properties similar to lidocaine but in contrast has a much greater oral activity and a long elimination half-life.[41]

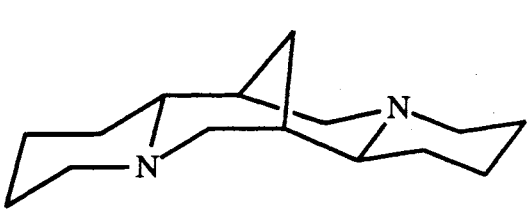
Flecainide (**2**) has been marketed in Germany since 1982 and represents the first fluorine-containing antiarrhythmic agent. Clinical efficacy studies have shown the compound to be effective in suppressing ventricular and supraventricular arrhythmias.[19] Electrophysiological studies have shown that its primary effect is to slow the rate of rise of the action potential.[52] Due to the minor effects on the duration of repolarization and marked prolongation of cardiac conduction, flecainide has been categorized as a class Ic antiarrhythmic drug.[11,41,52] After the preliminary results of the CAST study were made public, flecainide was removed from clinical use.[63,64]

Encainide (**1**) is a class Ic antiarrhythmic agent with combined electrophysiological effects of lidocaine and quinidine. These effects include rate-dependent decrease in V_{max}, a decrease in APD, and an increase of the ERP:APD ratio.[41] It has been proven effective in the treatment of ventricular and supraventricular arrhythmias.[41] Pharmacokinetic studies of encainide demonstrated the clinical importance of metabolites in antiarrhythmic drug action. The two main metabolites, *O*-demethyl- and 3-methoxy-

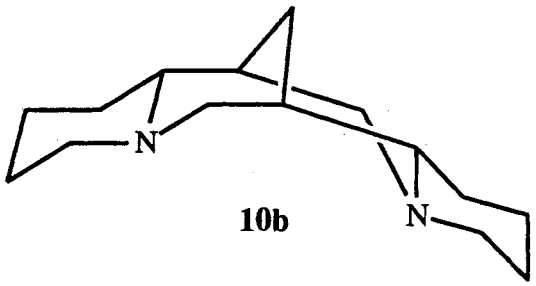
O-demethylencainide were found to be more potent in dog and rabbit hearts than the parent compound.[11,41] Low doses of *O*-demethylencainide produced effects similar to those with lidocaine (**7**) while the effects of encainide (**1**) resemble those of quinidine.[15,52] In view of the CAST study, it was concluded that the negative side effects of encainide outweighed the therapeutic benefit. Immediately after the results of the CAST study were made public, encainide (**1**) was removed from the market by the FDA. Other class I agents are currently undergoing a similar evaluation.

Lorcainide (**3**) has been used in some European countries since 1981 and belongs to the class Ic antiarrhythmic agents having local anesthetic properties. The electrophysiological studies show similarities to that with flecainide (**2**) in that the maximum rate of depolarization is reduced and the APD is prolonged. Metabolites of lorcainide have been identified but were not as active as these derived from encainide (**1**).[41]

Sparteine (**10a**) belongs to a group of naturally occurring lupine alkaloids and is categorized as a class I antiarrhythmic agent.[68] Pharmacological action of sparteine has been the subject of contradictory reports and it's antiarrhythmic activity has only recently been established.[11] Conclusions from the studies were that sparteine prolonged the APD



10a



10b

and showed an increase in the refractory period in rats.[11,68] The structure of sparteine **10a** is shown as the chair-boat conformation, but IR and NMR analysis concluded that in solution and in the liquid state conformer **10b** is also present.[76]

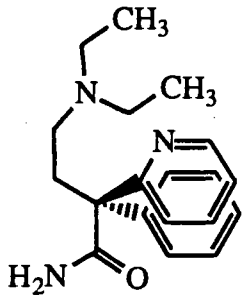
The inner rings of sparteine consist of a 3,7-diazabicyclo[3.3.1]nonane (called bispidine) moiety. Sparteine was shown to possess antiarrhythmic activity but the toxicity of the compound was high. It was believed that by changing substituents on the outer rings of sparteine with various groups to alter lipophilicity that the antiarrhythmic activity might be enhanced.[60] In 1977, a series of 3,7-dialkylbispidines were synthesized by Ruenitz and Mokler.[60] Testing of the compounds (using disopyramide as the clinical standard) employed a mouse-chloroform fibrillation assay. The results indicated that the potency of these agents was reasonably high, but the acute toxicities were a negative factor against their use as clinical agents.[60] Considering these results, slight structural modifications were incorporated into the framework of the bispidine system. Introduction of the *N*-benzamide functionality into compounds **11** had a dramatic effect (Table IV) upon the observed antiarrhythmic activity. Not only did these amides possess an increase in potency, but they were less toxic by more than two fold where compared to the dialkyl derivative cited earlier (Ruenitz and Mokler[60]). Several compounds were reported[61] but Table IV illustrates only the most active (more active than the standard disopyramide) of the series synthesized.[61]

Binnig developed several dispidine analogues **12** that were tested for antiarrhythmic activity in guinea pigs and found to be quite active where compared to quinidine (**4**).[9] Table V illustrates a few examples of the most active derivatives. Unexpectedly, these compounds and their salts possessed calcium-antagonistic, antiphlogistic and thrombocyte aggregation-inhibiting properties.[9]

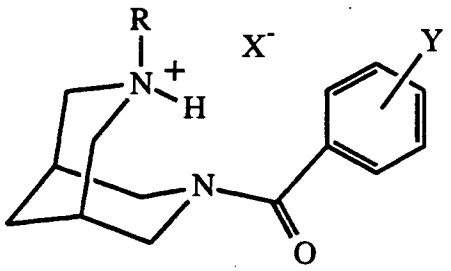
Several 3,7-diazabicyclo[3.3.1]nonanes (DNBCN) **13** were prepared with an alcohol or an ether functionality in the 9-position and showed enhanced activity (Table VI).[54] To assay for an antiarrhythmic effect, rats were pretreated intravenously with aconitine to induce arrhythmias. Tertiary amines **13** exhibited therapeutic activity several times more potent than lidocaine (**7**) with the added bonus of possessing a small amount of calcium antagonistic capability. Furthermore, it was noted that these agents had the capability

TABLE IV[a]

ANTIARRHYTHMIC ACTIVITY OF BENZAMIDE DERIVATIVES **11**



6 (Disopyramide)



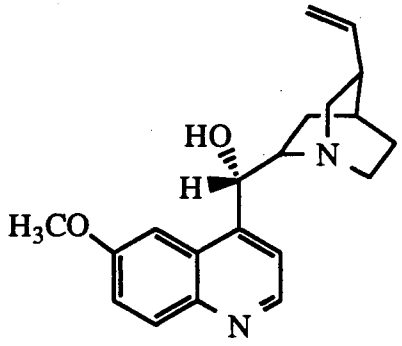
11

Agent[b]	R	Y	ED_{50}[c]	LD_{50}[d]	T. I.[e]
6			90	517	5.77
11a	CH_3	H	85	621	7.29
11b	CH_3	4-OCH_3	78	463	5.93
11c	CH_3	4-Cl	49	535	10.89

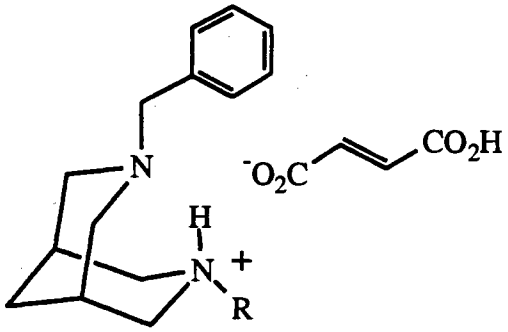
[a]Reference 61.
[b]Mouse-chloroform fibrillation assay in adult mice.
[c]ED_{50} = Effective dose (μmole/kg ip) in which 50% are affected; mean potency.
[d]LD_{50} = Dose (μmole/kg ip) causing mortality in 50% of mice; mean toxicity.
[e]Therapeutic Index (T. I.) = LD_{50}/ED_{50}.

TABLE V[a]

ANTIARRHYTHMIC PROPERTIES OF BISPIDINES **12**



4 (Quinidine)



12

Agent	R	ED_{50}[b]	Max. Effect Dose[c]	Toxic Dose[d]	Q[e]
4		42.7	215	464	10.9
12a	$CH_2C_6H_3$-3,4-$(Cl)_2$	15.6	215	464	29.7
12b	$CH_2C_6H_4$-4-F	20.2	100	215	10.6
12c	$CH(Ph)_2$	20.4	215	464	22.8

[a]Reference 9.

[b]Effective dose (mg/kg) for the increase by 50% in the duration of aconitine infusion.

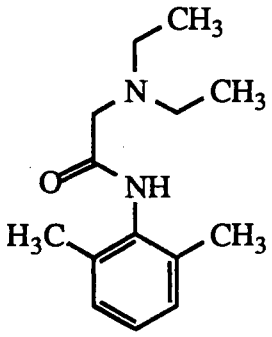
[c]Maximum tolerated dose (mg/kg) to achieve maximum duration effect.

[d]Dose (mg/kg) at which toxic side effects, such as cyanosis or electrocardiograph (ECG) change, occur.

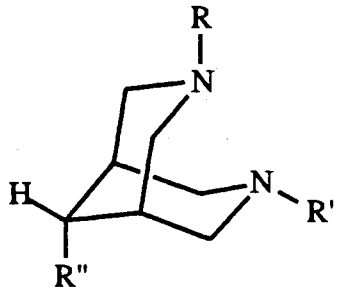
[e]Q = Toxic Dose/ED_{50}

TABLE VI[a]

ANTIARRHYTHMIC ACTIVITY OF BISPIDINES **13**



7 (Lidocaine)



13

Agent[b]	R	R'	R"	ED_{50}[c]	LD_{50}[d]	T.I.[e]	R.I.[f]
7				10.0	28.5	3	1
13a	CH_3	CH_3	O_2C-2-Naphthyl	0.11	17.0	154	58
13b	CH_3	CH_3	O_2CPh	0.08	9.0	112	39
13c	CH_3	CH_3	OC_6H_4-4-Cl	0.9	52.0	58	21

[a]Reference 54.
[b]Aconitine-induced arrhythmias in rats.
[c]Effective dose (mg/kg) to restore normal sinus rhythm in 50% of rats tested.
[d]Dose (mg/kg) causing mortality in 50% of tested rats.
[e]Therapeutic Index (T. I.) = LD_{50}/ED_{50}.
[f]Relative Index (R. I.) = T.I. (agent)/T.I. [lidocaine (**7**)].

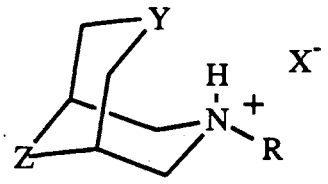
of increasing the stimulus threshold (better known as an increase in the refractory period). This type of effect can ultimately lead to the abolishment of certain types of cardiac arrhythmias.[11,54]

Our group has synthesized several 3-azabicyclo[3.3.1]nonane derivatives, and tested the antiarrhythmic efficacy using lidocaine as the standard.[8,13c] These agents were evaluated in dog models in which the heart was impaired with surgically-induced myocardial infarctions. Antiarrhythmic activity was judged on ability of the agent to alleviate sustained ventricular tachycardia (SVT) generated by programmed electrical stimulation (PES) of the damaged heart cells. Electrophysiological studies have shown that polar groups (such as carbonyls and alcohols) at the 9-position greatly reduce the antiarrhythmic capabilities of selected agents.[8] In contrast, ketal **14e** (X = ClO_4) and thioketal **14g** (X = ClO_4) had good activity compared to polar groups as previously mentioned. Table VII illustrates the most active compounds synthesized in our laboratory. Activity is described as ability of an agent to prevent SVT in terms of nonsustained ventricular tachycardia (NSVT). Although the activity of these compounds appears to be almost the same, salt **14d** (X = ClO_4) was found to suppress the heart rate by 29% and to inhibit the induction of reentry of the VT, relative to lidocaine [(**7**); suppressed heart rate by only 11%]. Interestingly, agent **14d** (X = ClO_4) increased the mean blood pressure which is an added feature since pressure decreases are commonly experienced during SVT. The electrophysiology and pharmacology of **14d** have been extensively studied.[13] Compound **14a** (X = ClO_4) also had a significant effect on the reduction of the heart rate in dog models.[58]

Most of the examples of bispidines cited possess very good antiarrhythmic activity, and one might conclude that more attention should be focused on derivatives within this basic framework. Trends in useful activities for a series of such compounds can be seen, but serious problems may arise when trying to compare agents that have been screened by different methodologies.

TABLE VII[a]

ANTIARRHYTHMIC ACTIVITY OF 3-AZABICYCLO[3.3.1]NONANES **14**



14

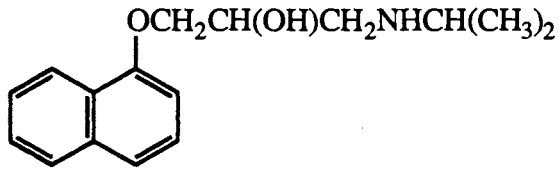
Comp[b]	R	Y	Z	(Effect on SVT[c]) 3 mg/kg	6 mg/kg
7 (lidocaine)				Reduced[d]	Reduced
14a	$CH(CH_3)_2$	NC(O)Ph	CH_2	NSVT[e]	NSVT
14b	$CH(CH_3)_2$	$NCH_2C_6H_4$-3,4$(OCH_3)_2$	CH_2	NSVT	NSVT
14c	$CH(CH_3)_2$	NCH_2Ph	CH_2	NSVT	NSVT
14d	NCH_2Ph	S	CH_2	NSVT	NSVT
14e	NCH_2Ph	S	$C(OCH_3)_2$	NSVT	NSVT
14f	NCH_2Ph	$CHCO_2Et$	CH_2	NSVT	NSVT
14g	NCH_2Ph	$CHCO_2Et$	$C(SCH_2)_2$	NSVT	NSVT
14h	NCH_2Ph	Se	CH_2	NSVT	NSVT

[a]Reference 8.
[b]X = ClO_4, Cl, Br, citrate, fumarate, HSO_4.
[c]SVT = Sustained ventricular tachycardia induced by programmed electrical stimulation (PES) of infarcted dog heart.
[d]Reduced sustained ventricular tachycardia.
[e]NSVT = Nonsustained ventricular tachycardia (or abolished VT).

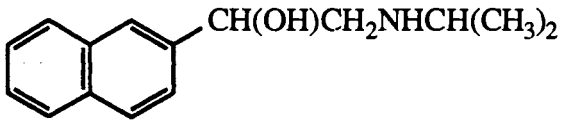
Most antiarrhythmic agents cited to this point appear to be primarily class I agents by the Vaughan Williams classification.[83] The CAST[51,63,81] study demonstrated some of the negative side effects (such as proarrhythmias) associated with certain class I drugs. With this evidence, many researchers have been prompted to consider the synthesis of agents that possess different modes of action, namely class II, class III, class IV, or combinations thereof.

Class II Antiarrhythmic Agents

The major electropharmacological effects of beta-adrenergic receptor blocking drugs (class II) is shunting the catecholamine-induced increase in automaticity.[52] Catecholamines play a critical role in the propagation of abnormal action potentials (e.g., during ischemia). Blockade of such effects might explain some of the responses observed with beta-adrenergic blocking drugs in the prevention of sudden cardiac death, bearing in mind that other explanations are also possible. A number of such agents are known, including propranolol (**15**) and pronetalol (**16**) which display quinidine-like properties in slowing the phase 0 upstroke velocity (slowing APD) at high concentration *in vivo*.[73]



15



16

Propranolol (**15**) is a class II antiarrhythmic agent which was introduced in 1964 for the treatment of anginia pectoris, cardiac arrhythmias, and hypertension.[15] Since that time, electrophysiological and pharmacological studies[11,15,52] of **15** have been extensive One particular action observed was the shortening of the APD *in vitro*[57] and in humans.[19]

Pronetalol (**16**) was found to possess properties similar to those of propranolol. A comparative study between **15** and **16** was carried out by Black[10] to determine which agent had the greatest effect as a class II antiarrhythmic agent. Propranolol is a more active sympathetic β-receptor antagonist while the metabolitic half-lives and LD_{50}'s of the two agents were found to be very similar.[18] In mice, the acute toxicity effects of pronetalol (**16**) were attributed to a nonspecific action on the central nervous system because the acute LD_{50}'s for the (S)-(+)-isomers (inactive) and (R)-(-)-isomers (active) were the same as that for the racemate.[10] Propranolol (**15**) was concluded to be a better antagonist (β-receptor) but was devoid of intrinsic sympathomimetic activity as judged by decreased resting heart rates in anesthetized cats.

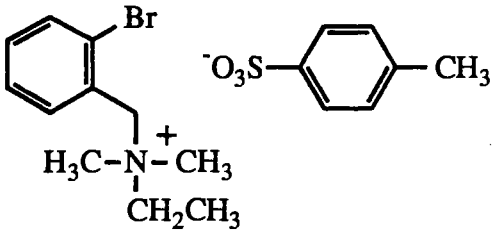
A detailed explanation on the design and use of β-blockers has been reviewed.[3] Recently researchers have concluded that agents which tend to shorten the APD are less attractive.[63,86] Today, antiarrhythmic drugs are designed with probable potential to prolong the action potential duration as is seen with class III agents.

Class III Antiarrhythmic Agents

In the treatment of life-threatening VT and ventricular fibrillation (VF), there exists a need for antiarrhythmic agents that express their salutary effects by prolonging repolarization (class III) rather than by strictly inhibiting myocardial conduction (class I) through blocking the fast sodium channels.[72] Numerous studies have indicated that prolongation of the APD and effective refractory period (ERP), without any change in the conduction velocity, support an important mechanism in the prevention and termination of developing atrial and ventricular fibrillation.[74] Many class III AAA possess the ability to prolong the APD and ERP, but the structures of most agents are quite heterogenous. The efficacy, potency, and antiarrhythmic spectrum of action are not uniform, and the ionic mechanisms by which the agents delay repolarization are also frequently different.

As a result, members of class III AAA vary markedly in their physiological profiles but appear to have in common the ability to prolong ventricular repolarization and ERP.

Bretylium (**17**), which has been labelled a prototype class III antifibrillatory drug, was originally introduced as an antihypertensive agent in 1959.[11] In the mid 1960's, **17** became the first drug shown to exert pronounced antifibrillatory effects as demonstrated in humans. The mechanism of action was suggested from the use of isolated Purkinje fibers and ventricular muscle in which the APD and ERP were both prolonged without altering the ERP/APD ratio.[40] By measuring the fibrillation threshold, it was possible to compare antifibrillatory action of several other antiarrhythmic agents and bretylium (**17**). Results indicated that bretylium (**17**) was the only agent to increase the threshold and also the only drug that was positively inotropic.[4] Inotropic agents produce an increase in cardiac output and central aorta pressure without impairing flow to regional circulation or producing unwanted arrhythmias.[15] Present FDA-approved bretylium (**17**) is used in the



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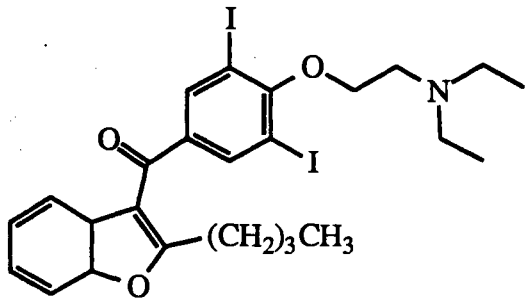


18

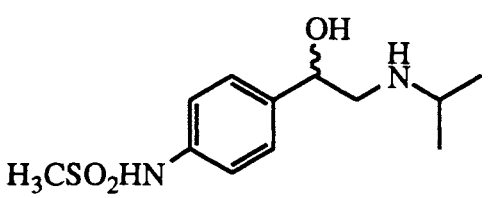
treatment of life-threatening ventricular fibrillation and tachycardia when first-line agents such as lidocaine (**7**) and procainamide (**5**) fail using normal doses.

An effective but rather nonspecific class III antiarrhythmic agent is amiodarone (**18**) which was initially developed for itsantianginal properties.[11] Control of ventricular and supraventricular tachyarrhythmias has been achieved with this potent agent, and amiodarone (**18**) is, in most cases, the only agent effective in controlling SVT.[66] The

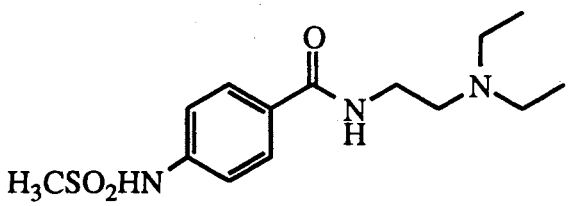
major electrophysiological effects of **18** are the prolongation of the APD in atrial and ventrical muscle and the ability to increase atrial, atrioventricular nodal, and ventricular effective refractory periods.[75] The effects on the sinus node function, as seen in the isolated rabbit preparation, is the prolongation of the APD where the drug's adrenergic blocking action contributes to the sinus slowing.[30]

A pure class III drug should not directly alter the conduction time (phase 0 upstroke) in cardiac tissue. Oral administration of **18** revealed an increase in the AH interval (parameter measured from ECG; AH interval represents the AV nodal conduction time) due to prolongation of atrial effective refractory periods, that is, in lengthening of the relative refractory periods of the atrioventricular node in response to a series of action potentials.[25] Other studies have shown that **18** induces slight increases in the HV and QRS intervals as revealed by detailed electrophysiological studies on the mechanism of action pertaining to the QT interval prolongation and the effect on ventricular arrhythmias.[31] These findings indicate that amiodarone (**18**) has more than just class III antiarrhythmic action, but the class II (β-blocking) activity is not as pronounced [53]

In 1960, the development of sotalol (**19**) was described, and it was found to be unique in that it possessed a combined class II (β-adrenergic blockers) and class III (similar to amiodarone) antiarrhythmic effects. Clinical trial studies of sotalol (**19**)



19



20

revealed significant electrophysiological effects by increasing the basic sinus length, sinus node recovery time, and the effective and functional refractory period of the atrioventricular node.[85] It was noted that these effects are consistent with class II agents,

and no class III action was observed. Echt and co-workers[20] compared intravenous sotalol (**19**) and intravenous propranolol (**15**) in 17 patients. Results indicated that **19** (but not **15**) prolonged atrial and ventricular effective refractory periods, lengthened the APD, and lengthened the QT interval. These findings affirm that sotalol (**19**) possesses both class II and class III antiarrhythmic activity.

Sudden cardiac death can be the end result of lethal ventricular arrhythmias as indicated earlier. Senges and co-workers[67] assessed the efficacy of sotalol (**19**) in 18 patients with SVT. In each patient, the arrhythmias were induced by PES in the controlled studies. Sotalol (**19**) prevented the induction of sustained VT in 12 of the 18 patients (67%) and therefore was considered an effective agent in the treatment of sustained ventricular tachycardia.

Currently there is no selective class III agent available for clinical use. Amiodarone (**18**), a class III agent, is a nonspecific drug and is the only one approved for therapeutic applications. However, recent reports have described the synthesis and biological activity of a number of potent and selective class III antiarrhythmic agents.[45,49]

Lumma and co-workers[45] prepared a series of benzamide derivatives in an attempt to achieve selective class III antiarrhythmic activity. Screening of the compounds [such as sematilide (**20**)] were carried out *in vitro* on isolated canine Purkinje fibers to determine the effects on APD at 95% repolarization (APD_{95}) and the maximum rate of repolarization (V_{max}). Active compounds must prolong APD_{95} and functional refractory period (FRP) by 20% (C_{20}) with a minimal effect on V_{max} in order to have selective class III electrophysiological action. All the compounds tested displayed no significant decrease in V_{max} and the conduction times were essentially unchanged.

Structure-activity relationships indicated that exchanging the methyl group on the sulfonamide moiety in **20** with another alkyl group greatly decreased the activity.[45] When the N-*H* hydrogen of the sulfonamide functionality was replaced with a methyl group, the activity was completely abolished. In view of its overall profile, including low

toxicity (LD_{50} ~ 250-300 mg/kg, ip, mouse), compound **20** (sematilide) was further developed for therapy involving ventricular arrhythmias.

A similar electrophysiological experiment, using isolated canine Purkinje fibers, was described by Morgan and co-workers[49] for a family of benzamides to determine their selective class III activity using sematilide (**20**) as a standard. As mentioned earlier, a compound is considered to have selective class III effects if it increases APD by 20% without causing a significant (≥10%) decrease in V_{max}. Results illustrated in Table VIII indicate that several of the agents tested have selective class III action with agent **21a** being equieffective for *in vivo* and *in vitro* models as compared to **20**.

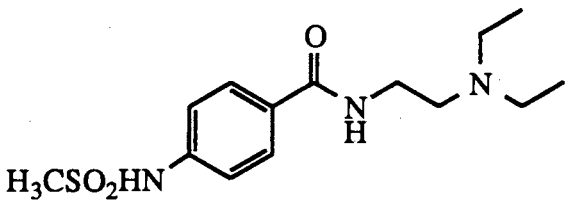
Structure-activity relationships indicate that the imidazole moiety can be a suitable replacement for the sulfonamide group to enhance class III AAA.[49] Substitutions on the imidazole ring resulted in active agents, but attachment of the imidazole functionality to the benzene ring via C(2) of the imidazole ring resulted in very weak class III activity relative to **21a**. Substitution of different groups in these benzamide systems also gave varied activities.

Many reseachers have focused attention on the synthesis of agents possessing specific characteristics. Recently some (aryloxy)propanolamine[12] derivatives and another family of benzamides[22] were reported. Testing of these agents was the same as described earlier[49] with the results that selected compounds in each series showed marked activity where compared to sotalol (**19**). Table IX and Table X illustrate the findings which led to the conclusion that **22a**, **22c** and **23a** possess potent and selective class III action with the ability to prevent SVT. These three agents were considered sufficiently effective to be submitted for clinical trials.

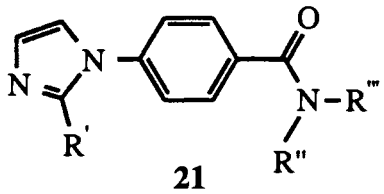
Along with compounds **21**, **22**, and **23** already mentioned, several others have demonstrated very good antiarrhythmic activity. These include agents **24** (E-4031),[55] **25** (ibutilide),[32] and **26** (MS-551)[38] all of which are in clinical trials. The antiarrhythmic

TABLE VIII[a]

INTRACELLULAR ELECTROPHYSIOLOGY OF
4-(1*H*-IMIDAZOLE-1-YL)BENZAMIDES **21**



20 (Sematilide)



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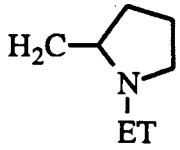
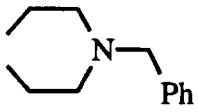
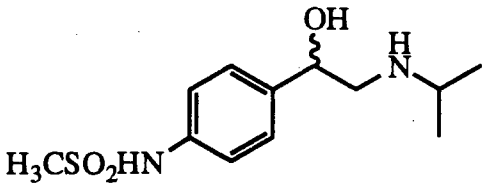
Comp	N[b]	R'	R''	R'''	C_{20} APD_{95} (μM) [Range][c]
20	18				4.4 [1.9-11]
21a	3	H	H	$CH_2CH_2NEt_2$	2.9 [2.2-3.4]
21b	4	CH_3	H	$CH_2CH_2NEt_2$	NR
21c	4	H	1-Naph	$CH_2CH_2NEt_2$	0.4 [0.2-0.6]
21d	4	H	H		3.0 [2.2-4.5]
21e	2	H			0.9 [0.7-1.0]

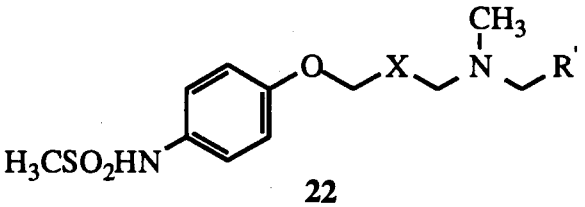
[a]Reference 49.
[b]Number of experiments.
[c]Concentration (interpolated) of test compound which caused a 20% increase in APD_{95}. Lowest and highest values given in brackets. NR = not reached.

TABLE IX[a]

ANTIARRHYTHMIC ACTIVITY OF (ARYLOXY)PROPANOLAMINES **22**



19 (Sotalol)



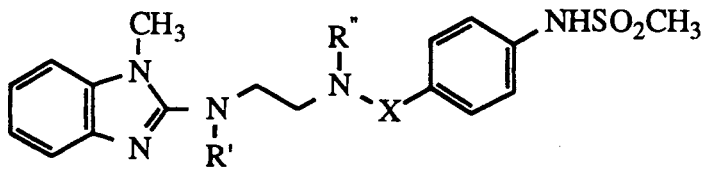
22

Comp	X	R'	dose mg/kg	N[b]	AERP[c]	ACT[d]
19			2.5 (iv)	5	42	-5
			5.0 (iv)	5	57	-7
			10.0 (iv)	5	68	-4
22a	CHOH	quinolin-2-yl	5.0 (iv)	5	45	-9
			10.0 (id)	5	31	-4
22b	CH_2	quinolin-2-yl	5.0 (iv)	2	52	-6
22c	CH_2	6-[(methylsulfonyl)-amino]quinolin-2-yl	0.05 (iv)	3	53	-5
			0.25 (iv)	3	70	-4

[a]Reference 12.
[b]Number of experiments.
[c]AERP: atrial effective refractory period.
[d]ACT: atrial conduction time.
[e]Data reported as percent change from pre-drug state.

TABLE X[a]

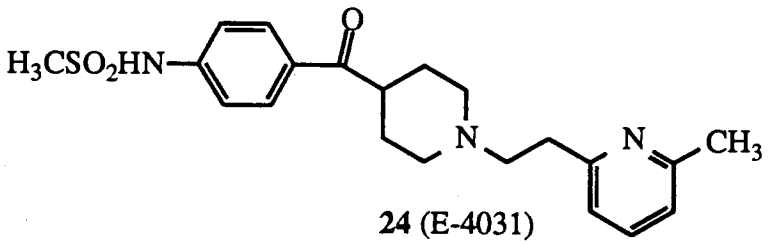
ANTIARRHYTHMIC ACTIVITY OF BENZAMIDES **23**



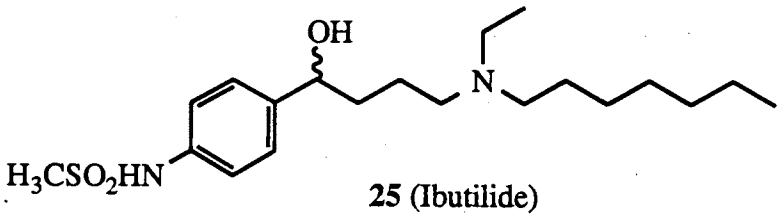
23

Comp	X	R'	R"	dose mg/kg	N[b]	AERP[c]	ACT[d]
19 (sotalol)				2.5	5	42	-5
				5.0	5	57	-7
23a	SO_2	CH_3	CH_3	1.0	5	40	-6
				2.5	5	53	-5
23b	CO	CH_3	CH_3	1.0	2	18	-1
				5.0	2	44	-3
23c	SO_2	CH_2-CH_2		1.0	2	22	3
				5.0	2	40	-3
24d	CO	CH_2-CH_2		1.0	5	33	-10
				5.0	5	63	-10

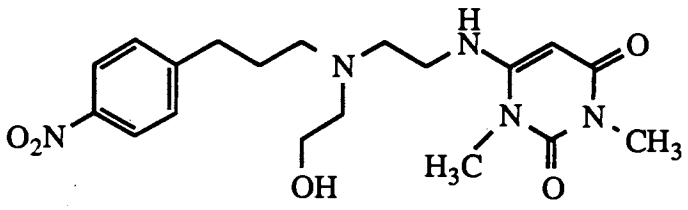
[a]Reference 22.
[b]Number of experiments.
[c]AERP: atrial effective refractory period.
[d]ACT: atrial conduction time.
[e]Data reported as percent change from pre-drug state.



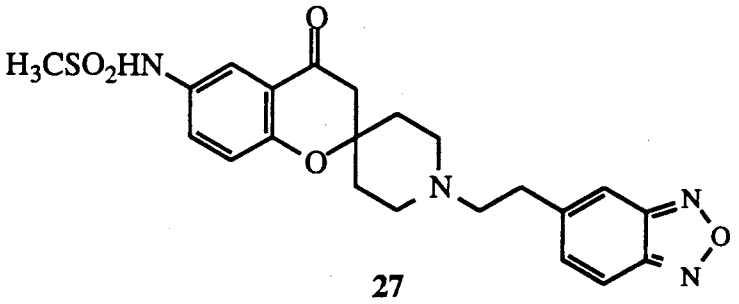
24 (E-4031)



25 (Ibutilide)



26 (MS-551)



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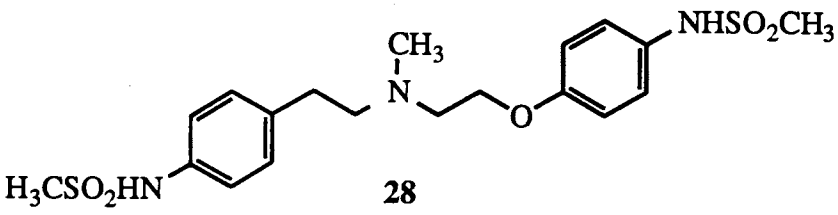

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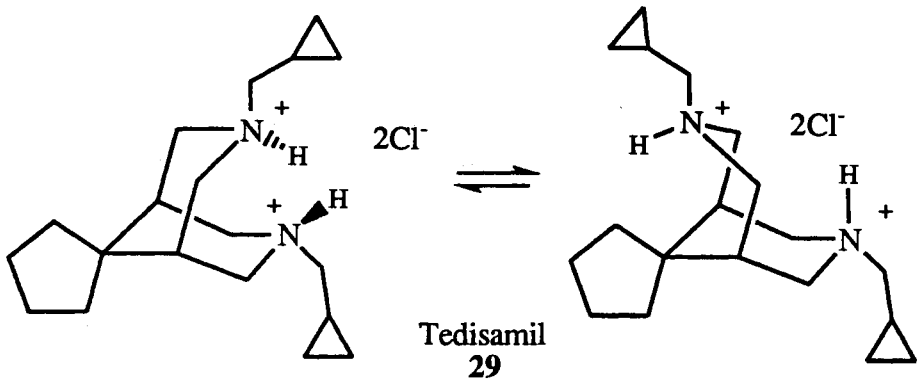
activities of the three have been found to be similar to that of sotalol (**19**) but most have a higher efficacy. The literature contains many agents which have shown excellent class III action, but most are *not* presently in clinical trials because the activity displayed was less than that of **19**. Examples are certain spiro derivatives[23] **27** and certain bis(arylalkyl)-amine[17] compounds **28**. Since the CAST study, there has been a surge towards the development of drugs with *selective* class III action.

Recently, a new antiarrhythmic agent, tedisamil (**29**), belonging to the family of



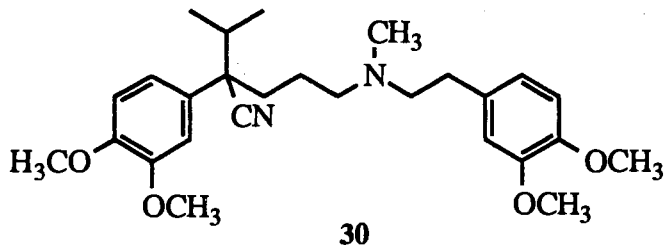
Tedisamil
29

3,7-diheterabicyclo[3.3.1]nonanes (DHBCN), was found to have slight class I action but predomin-ately class III activity. Tedisamil (**29**) prolonged the APD, the QT interval, and the refractory period and thus followed the criteria for class III action.[7] Structure-activity relationships of this compound were not totally described, however, and there was no rationale for the observed class III action. Many antiarrhythmic agents in the family of DHBCNs previously reported[8,9,54,60,61] were stated to possess only class I activity. For this reason the basic 3,7-diheterabicyclo[3.3.1]nonane ring structure cannot be totally responsible for the observed class III action. One reasonable explanation is the presence of the spiro ring across the 9-position or the cyclopropylmethyl groups in the 3- and 7-positions. It is not known if 29 has a CC⇄CB equilibrium in solution but it is likely so from other work in our laboratory.

Class IV Antiarrhythmic Agents

Calcium antagonists are widely recognized as agents with a great impact on both pharmacology and clinical therapy for cardiovascular disease and are classified as class IV antiarrhythmic agents. These drugs terminate paroxysmal supraventricular tachycardia (sudden onset and termination of arrhythmias that are triggered by ventricular premature contractions) and control the ventricular response to atrial flutter and fibrillation.[52] Cardiac arrhythmias result from disorders of impulse conduction and formation, or a combination of both mechanisms. Salutary effects of these agents in supraventricular arrhythmias are believed to be due to the slowing down of the Ca^{+2} channel-dependent conduction in the AV node with a prolongation of AV nodal refractory period.[65] Control of ventricular arrhythmias by a calcium antagonist is still speculative. In patients with ischemic heart desease (myocardial impairment due to imbalance between coronary blood flow and myocardial requirements caused by changes in coronary circulation), such agents prevent genesis of certain dysrhythmias by reversing coronary vascoconstrictions which possibly may prevent the incidence of sudden cardiac death.[65]

Verapamil (**30**) is considered the best example of a class IV (calcium antagonist)



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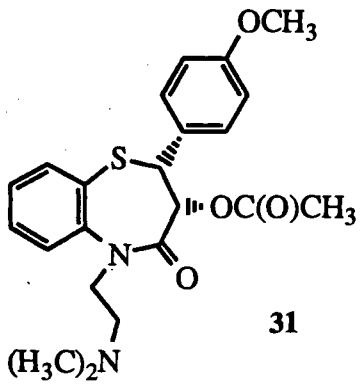

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antiarrhythmic agent (Table XI). Electrophysiological effects[70] of verapamil (**30**) are noted as described above in which the slow inward current carried by calcium is blocked.

TABLE XI[a]

ELECTROPHYSIOLOGICAL ACTIONS OF
VERAPAMIL (30) AND DILTIAZEM (31) IN HUMANS

Action ECG intervals	Verapamil (30)	Diltiazem (31)
Sinus rate	-	-
P-R interval	++	+
A-H[b] interval	+++	++
H-V[b] interval	0	0
QRS	0	0
Q-T interval	0	0
Atrial ERP[b]	0	0
AVN[b] RP	+++	++
Ventricular RP	0	0
Ventricular automaticity	0	0

[a]Reference 84.
[b]A, atria; H, His; V, ventricular; RP, refractory period; AVN, atrioventricular node; other electrocardiograph (ECG) intervals have the usual connotations: +, increase; -, decrease; 0, no effect.

This agent has received much attention, and the results of pharmacology studies are well documented.[16] Another agent which possesses very similar action to that of verapamil (**30**) is diltiazem (**31**). The electrophysiology and pharmacology data on **31** have shown this agent to be a selective class IV antiarrhythmic agent.[11,26] Table XI[84] illustrates the overall electrophysiological actions of the Class IV antiarrhythmic agents **30** and **31**.

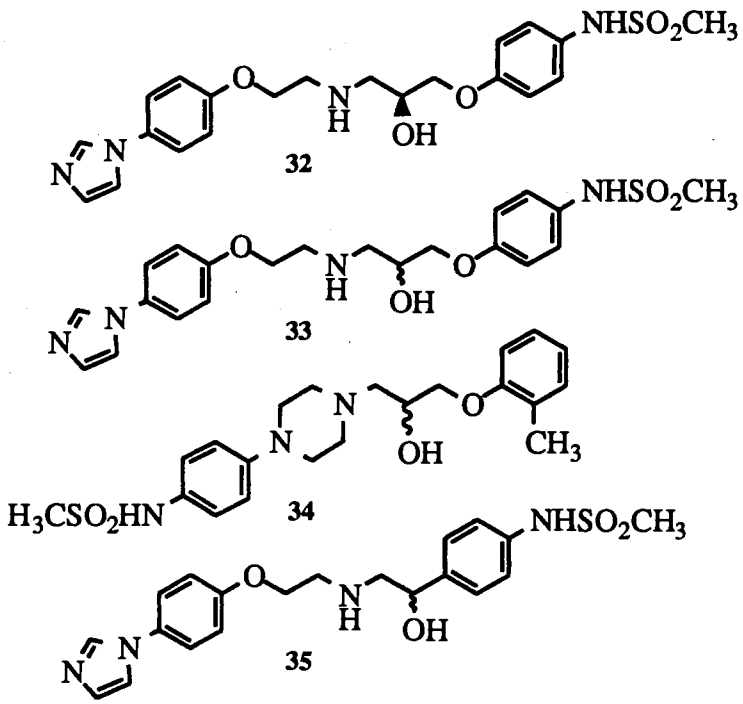
Antiarrhythmic Agents Possessing Multiple Class Action

One of the newest trends in the synthesis of more potent antiarrhythmic agents is to introduce a combination of different class actions into one molecule. The literature has only revealed the preparation of single agents possessing both class II and class III activity. Broader therapeutic benefits are the proposed major advantages to be expected for these types of drugs. Such compounds could have potent class III action and balanced β-blocking (class II activity) effects without significantly affecting cardiac conduction. Ideally, these agents would be potentially useful against reentrant and catecholamine-dependent arrhythmias at doses *below* those causing β-blocking-mediated hypotension and cardiac depression.[11,15] One characteristic action of class II agents is the slowing of heart conduction. β-Blockers enhance the depression of conduction at higher dosages but exert a much diminished effect at lower concentrations.[15,52]

Lis and co-workers[44] reported a series of (aryloxy)propanolamines possessing class II/III antiarrhythmic activity. Several compounds were tested, and the results indicated that agents **32** (S-isomer), **33**, **34**, and **35** had good efficacy [compared to other derivatives of **33-35**] even as racemic mixtures (Table XII). These agents prolonged the APD and had minimal effects on the rate of rise of phase 0 of the action potential (V_{max}). β-Receptor selectivity was determined using canine cardiac tissue in which varied activity was observed.[44] Compounds **32-35** were chosen in view of their established and useful pharmacological profiles.[44] Drug efficacy was determined using mongrel dog models (Table XII). These studies concluded that agent **32** (S-isomer) was more potent

TABLE XII[a]

ANTIARRHYTHMIC EFFICACY OF **19** AND **32-35**



Comp	no. eff.[b] / no. tested	dose range mg/kg, iv	eff. dose[c] mg/kg, iv	HR[d]	BP[e]	FRP[f]
19 (sotalol)	7/9	0.3-10	1.0 (3)	-6	8	14
32	7/8	0.1-3.0	0.3 (6)	-2	4	5
33	8/8	0.3-3.0	1.0 (5)	9	3	13
34	5/6	1.0-10	1.0 (4)	-3	13	8
35	7/8	1.0-10	1.0 (4)	1	-4	15

[a]Reference 66.

[b]Number of animals in which sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF) was not inducible after drug administration for the number of animals tested.

[c]Effective dose of the test compounds and the number of animals for which this dose was effective in parenthesis.

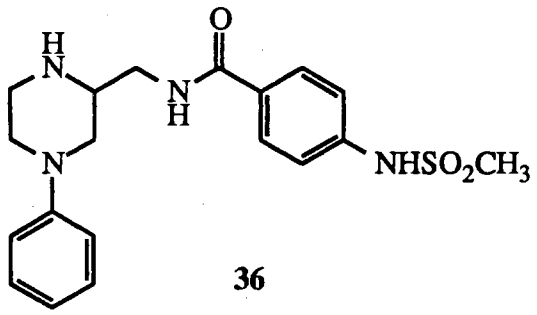
[d]Percent change in heart rate from control at effective dose.

[e]Percent change in blood pressure from control at effective dose.

[f]Percent change in function refractory period (FRP) from control at effective dose.

than sotalol (**19**), which was used as a standard, and merit further investigation as a combined class II/III antiarrhythmic drug.

Arylpiperazine derivatives of **36** were recently reported[56] to contain multiple class action as described previously.[44] These compounds possessed activity similar to agent



36

32, but the efficacy was less pronounced. It was noted that structural modification was probably needed to obtain more potent agents.[44]

Most of the agents reported herein do not possess only one mode of action. Several agents are classified in one category but show slight effects of the other classes. From experimental evidence, it is clearly evident that more work is needed to prepare agents with multiple class action. Compound **32** shows good promise as a therapeutic AAA due to its selective action and low toxicity levels.[44]

From the evidence given herein, the latest developments in AAA have been the incorporation of multiple class action into a single compound. Most of the limited work has focused on the development of agents possessing class II/III some of which have shown promise as effective antiarrhythmic drugs.[44,56] Recently, Hondeghem and Snyders[34] made suggestions on the development of antiarrhythmic drugs with novel electrophysiological profiles. They hypothesized that an ideal drug would have the ability to block the fast sodium channel with fast diastolic recovery (class Ib) and use dependent prolongation of the APD, that is, the agent would only prolong the action potential at an accelerated heart rate. Agents which block the potassium channel are

indicated as having use dependent prolongation of the action potential duration.[34] The term use dependence implies that the agent prolongs the action potential at accelerated heart rates with no prolongation of the APD observed at lower heart rates.

Biological Data of 3,7-Diheterabicyclo[3.3.1]nonanes

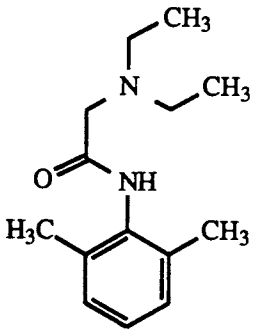
Some 3,7-diheterabicyclo[3.3.1]nonanes (DHBCNs) have reported good anti-arrhythmic activity as described earlier.[8] It was recently suggested that certain antiarrhythmic properties of these class Ib agents could originate from the inhibition of myocardial Na^+, K^+-ATPase activity.[13a] Chemical structure and lipophilicity have also been reported to have a strong influence on Na^+, K^+-ATPase[13a] and DHBCNs are lipophilic. The DHBCNs were tested using guinea pig myocardial Na^+, K^+-ATPase and Mg^{+2}-activated ATPase in comparison to lidocaine (**7**) and tedisamil (**29**). The inhibitory effects of these agents are significant and interesting in many respects. As previously mentioned, compound **14d** was found to increase blood pressure during sinus rhythm. Increased blood pressure may be explained by the inhibitory effects **14d** has on the Na^+, K^+-ATPase activity.[13a] Inhibitory effects on ATPase activity correlates well with the retention time in reversed-phase HPLC and the molar refractivity (MR) of the DHBCN derivatives (Table XIII). Greater inhibitory effects on the Na^+, K^+-ATPase activity were seen with lower MR values. The nonpolar nature of these compounds is measured by log P values in which the nonpolarity is relatively proportional to the retention time in reversed-phase HPLC. Lipophilic properties often play an important role in the inter-action between the therapeutic agent and the receptor site. More interaction between a specific receptor and the agent was found with the less polar compounds.[13a] Compound **44** was the only agent that possessed specific inhibition of Mg^{+2} activated ATPase. This type of activity may coincide with the DHBCN chelating properties with Mg^{+2}. Significant inhibition on myocardial Mg^{+2}-activated ATPase may be associated with the Na/Mg exchange to the intracellular Mg^{+2} ions of the myocardial cells.[13a] More effort in

TABLE XIII[a]

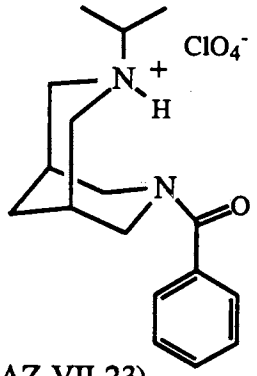
MOLAR REFRACTIVITY (MR), LOG P, RETENTION TIME (RT), AND IC_{50}[b] FOR DHBCN DERIVATIVES Na^+,K^+-ATPase AND Mg^{++}-ATPase ACTIVITIES (MEAN ± SD; n = 6)

Compds	MR	RT		IC_{50} for Na^+,K^+ ATPase (nM)[c]	IC_{50} for Mg^{++} ATPase (nM)[c]
		log P	(min)		
7 (lidocaine)	7.17	2.26	24.30	0.547 ± 0.041	0.433 ± 0.027
14a (SAZ-VII-23)	7.95	0.75	11.35	1.219 ± 0.125	1.217 ± 0.103
14b (GLG-III-93)	9.15	1.79	18.06	0.702 ± 0.074	0.426 ± 0.054
14d (BRB-I-28)	6.96	2.31	15.85	0.789 ± 0.047	0.324 ± 0.040
29 (tedisamil)	9.50	3.95	15.91	0.792 ± 0.060	0.378 ± 0.010
37 (GLG-IV-17)	8.24	2.48	24.30	0.547 ± 0.041	0.433 ± 0.027
38 (GLG-IV-57)	8.61	0.49	20.49	0.618 ± 0.023	0.433 ± 0.049
39 (GLG-III-70)	8.77	1.68	15.87	0.744 ± 0.055	0.507 ± 0.035
40 (SAZ-VII-22)	8.44	1.54	16.53	0.776 ± 0.036	0.501 ± 0.076
41 (GLG-IV-74)	9.65	-0.08	6.03	1.315 ± 0.103	1.010 ± 0.060
42 (GLG-III-96)	8.28	0.88	11.78	1.341 ± 0.130	1.137 ± 0.103
43 (GLG-III-86)	10.52	1.78	9.91	1.562 ± 0.105	0.810 ± 0.063
44 (GLG-IV-44)	8.32	0.08	7.50	no signif. effect	1.771 ± 0.049

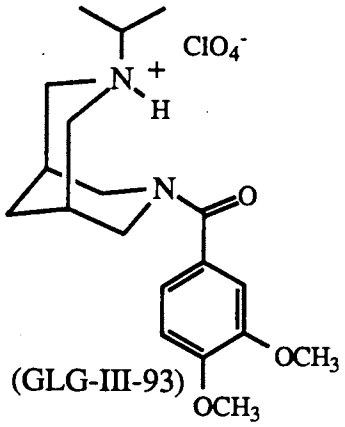
[a]Reference 13a
[b]IC_{50} = Concentration required to inhibit 50% of the enzyme activity.
[c]nM = 10^{-9} moles/liter.



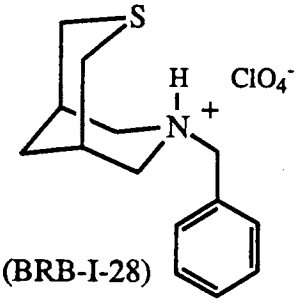
7 (Lidocaine)



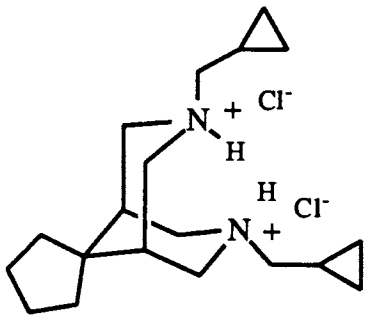
14a (SAZ-VII-23)



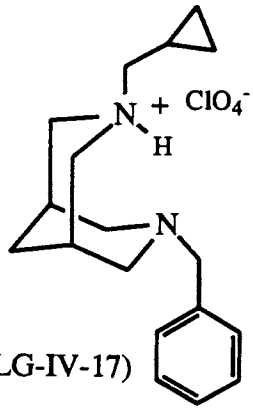
14b (GLG-III-93)



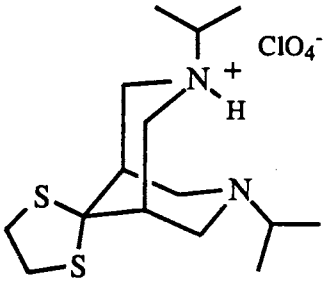
14d (BRB-I-28)



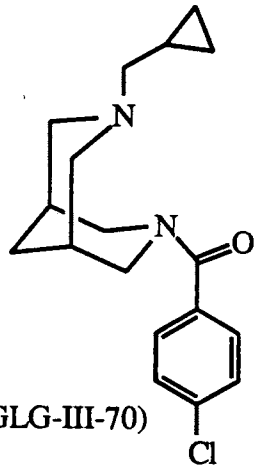
29 (Tedisamil)



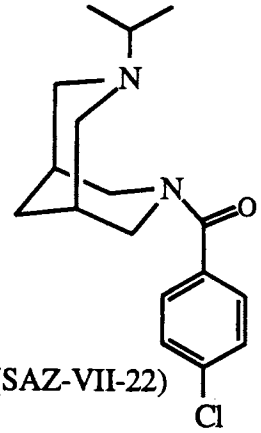
37 (GLG-IV-17)



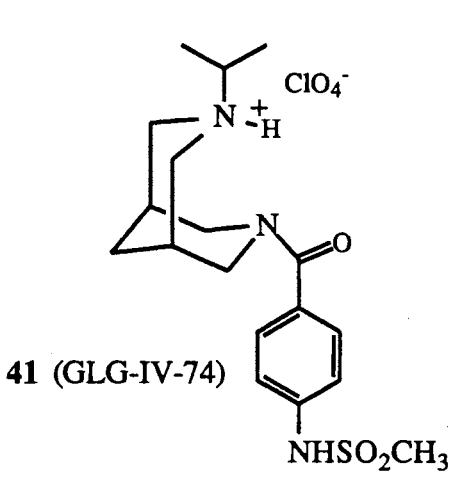
38 (GLG-IV-57)



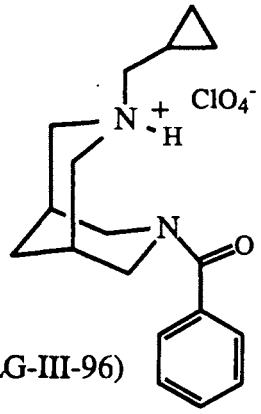
39 (GLG-III-70)



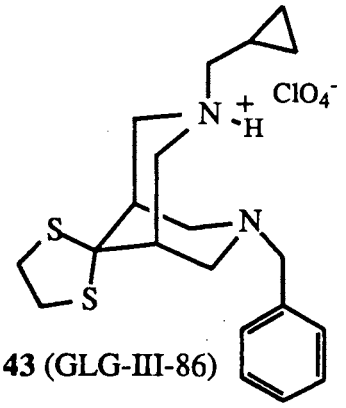
40 (SAZ-VII-22)



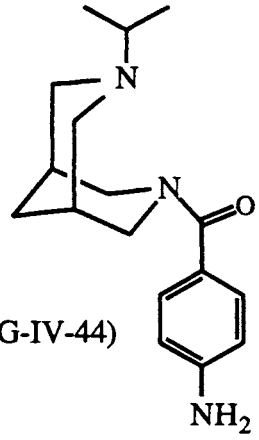
41 (GLG-IV-74)



42 (GLG-III-96)



43 (GLG-III-86)



44 (GLG-IV-44)

searching for specific Mg^{+2} ATPase inhibitors is warranted since no agents of this type are currently available.[13a]

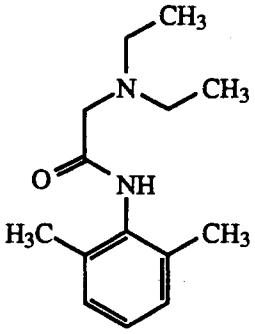
Interestingly, lidocaine (**7**) and tedisamil (**29**) were found to possess similar results as compared to the DHBCN derivatives in terms of Na^+,K^+-ATPase and Mg^{+2}-ATPase activities. Specific inhibitory effects and their relationship with respect to electrophysiological actions are yet to be determined. These AAA (**14a**,**41**,**42**,**44**) produced a significant inhibition on myocardial Mg^{+2}-activated ATPase and could lead to a possible link between Na/Mg exchange and intracellular Mg^{+2} ions of the myocardial cells.[13a]

Several members of the 3,7-diheterabicyclo[3.3.1]nonanes have displayed potent antiarrhythmic activity with low toxic and low proarrhythmic effects.[8] These results might suggest that more attention be focused on this area. From such model systems, examined to date, it should be possible to design more potent AAA considering the structure-activity relationships uncovered thus far.

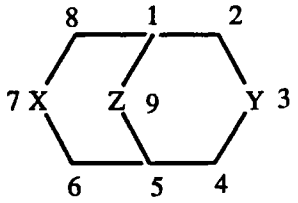
CHAPTER II

RESULTS AND DISCUSSION

Several members of the 3,7-diheterabicyclo[3.3.1]nonane (DHBCN) family have been found to exhibit good pharmacological properties in a variety of assays which are used to demonstrate such activity.[8,9,54,60,61] This group of heterocycles has displayed excellent antiarrhythmic action in the 1-4 day infarcted dog heart with the use of lidocaine (**7**) as the clinical standard.[8] Canine cardiovascular systems are considered the



Lidocaine
7



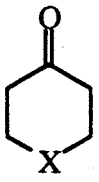
DHBCN

closest models for these assays in comparison to the human cardiovascular system. Any ability that these agents demonstrate in preventing lethal arrhythmias, which could result in sudden cardiac death, is meritorious. Presently, DHBCNs are known to possess class I activity, and testing for other class actions in this family is only now being initiated.[24]

Slight structural modifications in the 3- and 7-positions of DHBCN can significantly alter the observed class I antiarrhythmic activity.[8,9,60,61] Introduction of specific

functional groups can be effective in providing agents with more than one mode of action.[44,56] Further structural modifications might enhance antiarrhythmic activity in this family of heterocycles.

One ancilliary objective of this research was to develop methodology to obtain a series of 3,7-diheterabicyclo[3.3.1]nonan-9-ones which could be converted to 3,7-diheterabicyclo[3.3.1]nonanes and hydroperchlorates for the determination of potential antiarrhythmic activity. A modified Mannich type condensation, starting with ketones **45a** and **45b,** made it possible to prepare 3,7-diheterabicyclo[3.3.1]nonan-9-ones **46a** and

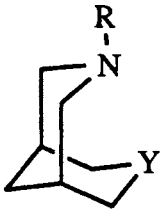


45

	X
a	$NCH(CH_3)_2$
b	NCH_2Ph

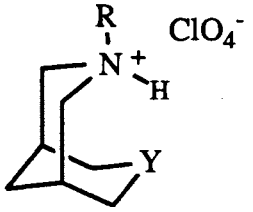
46

	X	Y
a	$NCH(CH_3)_2$	$NCH(CH_3)_2$
b	NCH_2Ph	NCH_2-cPr



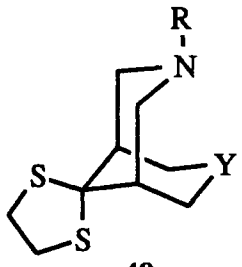
47

	R	Y
a	$CH(CH_3)_2$	$NCH(CH_3)_2$
b	CH_2-cPr	NCH_2Ph
c	CH_2-cPr	NH

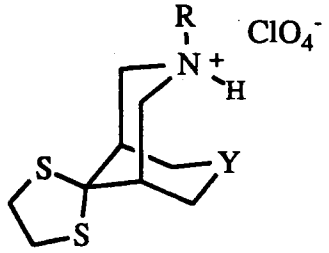


	R	Y
37	CH_2-cPr	NCH_2Ph
48	$CH(CH_3)_2$	$NCH(CH_3)_2$

46b. Reduction of the ketones led to the corresponding amines **47a** and **47b** and the respective hydroperchlorates **37** and **48**. Masking of the carbonyl has been found to aid in the antiarrhythmic properties of specific agents.[8] Thioketals **49a** and **49b** were synthesized using standard conditions along with the corresponding hydroperchlorates



49



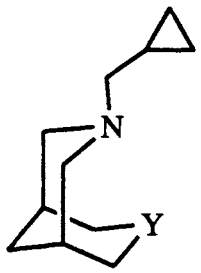
R	Y
a $CH(CH_3)_2$	$NCH(CH_3)_2$
b CH_2-cPr	NCH_2Ph

R	Y
38 $CH(CH_3)_2$	$NCH(CH_3)_2$
43 CH_2-cPr	NCH_2Ph

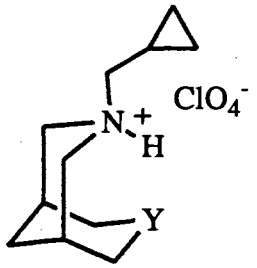
38 and **43**, respectively. Interestingly, thioketal salt **38** possessed excellent activity and is presently undergoing further testing.

Another major objective was to synthesize a series of amides and certain salts with varying substituents on the aromatic ring and at the 7-position in the bicyclic ring. Possibly, these modifications might enhance the antiarrhythmic activity. It had been speculated that the amide group would increase hydrophilicity of an agent for better drug formulation.[61]

Amides **39** and **50** were prepared using amine **47c**, and hydroperchlorates **42** and **51** were also obtained from their respective amides **50** and **39**. Amide **39** has been found to have good class Ib antiarrhythmic activity in dog models and possesses some moderate class III action as well.[29]

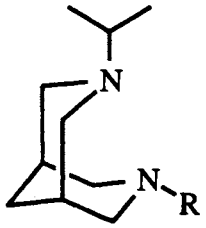


Y
39 $NC(O)C_6H_4$-4-Cl
50 NC(O)Ph



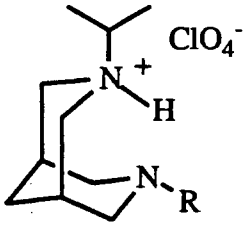
Y
42 NC(O)Ph
51 $NC(O)C_6H_4$-4-Cl

Another series of amides **52a**, **52d**, and **52f** was prepared with substituents (NO_2, F) in the *para* position of the aromatic ring. Additional reactions were carried out on amides **52a**, **52d**, and **52f** which produced several amides [**44**, **52b, c, e, g, h, i**] with greatly

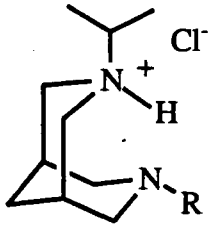


R
44 $C(O)C_6H_4$-4-NH_2
52a $C(O)C_6H_4$-4-NO_2
52b $C(O)C_6H_4$-4-$NHC(O)CH_3$
52c $C(O)C_6H_4$-4-$NHSO_2CH_3$
52d $C(O)C_6H_4$-4-F
52e $C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)
52f $C(O)CH_2C_6H_4$-4-NO_2
52g $C(O)CH_2C_6H_4$-4-NH_2
52h $C(O)CH_2C_6H_4$-4-$NHC(O)CH_3$
52i $C(O)CH_2C_6H_4$-4-$NHSO_2CH_3$
52j H

varied substituents. Most of the amides were converted to their respective hydroperchlorates [**41**, **53a, b, c, d, e, f**] though a few hydrochlorides (**54a**, **54b**, **54c**) were obtained. Amides **53c** was found to have excellent antiarrhythmic activity and possessed multiple class antiarrhythmic action in dog models.[29]

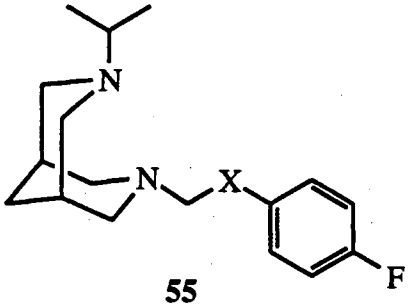


R
41 $C(O)C_6H_4$-4-$NHSO_2CH_3$
53a $C(O)C_6H_4$-4-$NHC(O)CH_3$
53b $C(O)C_6H_4$-4-F
53c $C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)
53d $C(O)CH_2C_6H_4$-4-NO_2
53e $C(O)CH_2C_6H_4$-4-$NHC(O)CH_3$
53f $C(O)CH_2C_6H_4$-4-$NHSO_2CH_3$



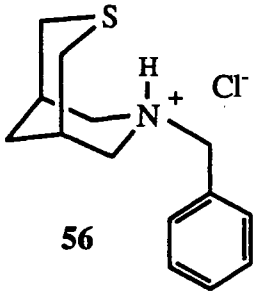
R
54a $C(O)C_6H_4$-4-NH_2
54b $C(O)C_6H_4$-4-NO_2
54c $C(O)C_6H_4$-4-$NHSO_2CH_3$

We have developed methodology for the alkylation of certain secondary amines to give *N*-alkyl derivatives of DHBCN. Reaction of **52j** with the 4-F-$C_6H_4C(O)CH_2Cl$



55

X
a C(O)
b CHOH



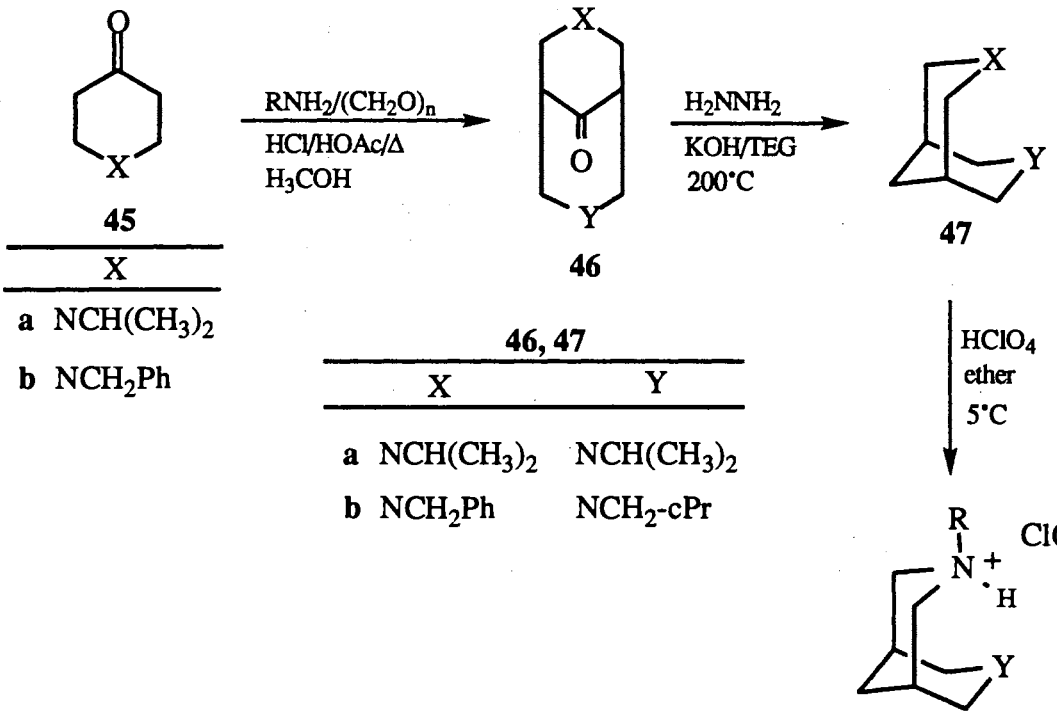
56

gave **55a** which was reduced to racemic alcohol **55b**. Alcohol **55b** is hypothesized to have multiple class AAA. Hydrochloride **56** was also prepared for comparison of its antiarrhythmic activity with that of the known hydroperchlorate **14d**.

Synthetic Methodology

A double Mannich condensation[62] of ketones **45a** and **45b** was utilized (Scheme I) to prepare 3,7-diheterabicyclo[3.3.1]nonan-9-ones **46**. Condensation of **45a** or **45b**, a primary amine, paraformaldehyde, acetic acid, and one half an equivalent (with respect to the amine) of conc HCl gave (after workup) ketone **46a** (69.1%) isolated as a yellow oil

SCHEME I



45

X
a $NCH(CH_3)_2$
b NCH_2Ph

46

46, 47

X	Y
a $NCH(CH_3)_2$	$NCH(CH_3)_2$
b NCH_2Ph	NCH_2-cPr

47

	R	Y
37	CH_2-cPr	NCH_2Ph
48	$CH(CH_3)_2$	$NCH(CH_3)_2$

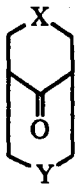
and **46b** (76.1%) as a crystalline solid. It had been previously discovered that the addition of HCl increased the yield of ketones prepared by the Mannich condensation from 25% to 56%.[89] It is speculated that the pH plays a critical role in the reaction kinetics, perhaps in accelerating formation of the intermediate iminium ion. Recently, it was found that the addition of a second equal portion of paraformaldehyde after 10 h of reflux increased the isolated yields of **46** from 56-57% to 69-76%. This phenomenon is not completely understood, but one possible explanation might be that some paraformaldehyde is removed during the reaction via the formation of side products.

Wolff-Kishner reduction of ketones **46** in the presence of KOH, hydrazine (95%), and triethylene glycol at high temperature (~200°C) gave amines **47a** and **47b** as oils. Characterization of these amines via NMR and IR analyses was completed, and the oils were used without further purification. Salts **37** and **48** were obtained upon treatment of a chilled (~5°C) solvent solution of **47a** or **47b** with $HClO_4$ (60%).

Modified conditions for the double Mannich reaction were employed to prepare reported ketones **57** to determine if isolated yields could be increased. Ketones **57a**, **57b**,

TABLE XIV

ISOLATED YIELDS OF KETONES **57a**, **57b**, AND **57c** BY PREVIOUS AND NEW METHODS



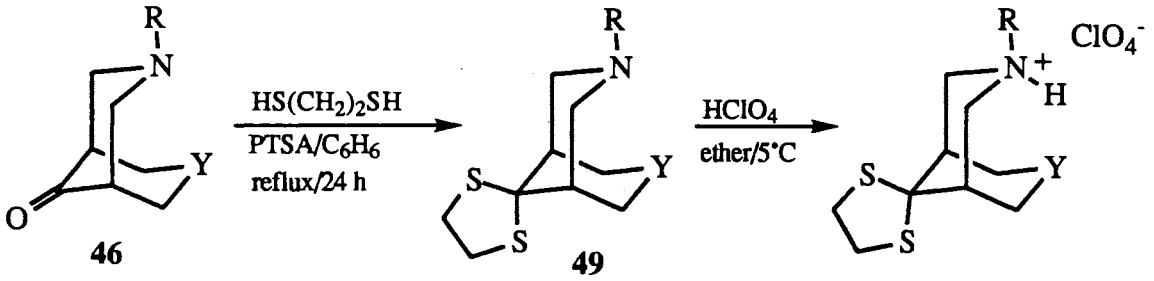
	X	Y	Previously reported yield	Yield obtained by new method
57a	$NCH(CH_3)_2$	NCH_2Ph	57.2%[a]	73.5%
57b	NCH_3	NCH_2Ph	45.0%[b]	72.8%
57c	NCH_2Ph	NCH_2Ph	58.2%[c]	69.1%

[a]Reference 89. [b]Reference 6. [c]Reference 9a.

and **57c** were all synthesized with isolated yields being increased by as much as 30% (Table XIV) or more.

Masked derivatives **49** from ketones **46** were prepared as shown in Scheme II with water being removed via a Dean-Stark trap. Thioketals **49** were isolated as oils which were quickly characterized and converted immediately to hydroperchlorates **38** and **43** (in the usual manner) in isolated yields of 29.3% and 40.6%, respectively. These modest

SCHEME II



46 **49**

46, 49

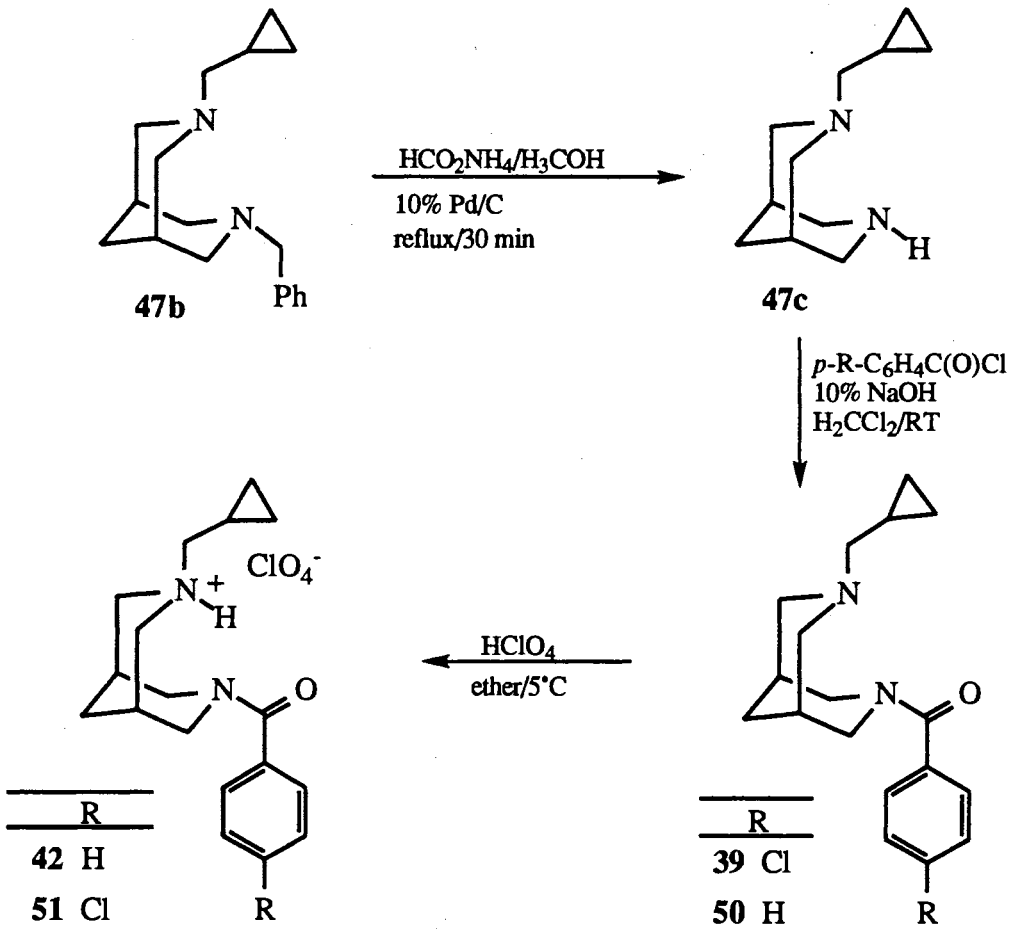
	R	Y
a	$CH(CH_3)_2$	$NCH(CH_3)_2$
b	CH_2-cPr	NCH_2Ph

	R	Y
38	$CH(CH_3)_2$	$NCH(CH_3)_2$
43	CH_2-cPr	NCH_2Ph

yields are possibly due to impurities that are present in the thioketals **49** prior to salt formation. The salts precipitated out of solution while protonated precursors to **38** and **43** were possibly soluble in the solvents.

In our work, several new amide derivatives were anticipated to have potential AAA due to earlier reports of amides possessing this activity.[9,61,89] Debenzylation of **47b** was effected with ammonium formate and Pd/C (10%) in boiling methanol to give the secondary amine **47c** as an oil (91.8%) which was used without further purification after spectroscopic identification. Ammoniun formate acts as a hydrogen source in the reaction, and this method (Scheme III) has only been recently examined.[59,89] The order of addition seems to be very important in this reduction. After the Pd/C is placed in the flask and the system is flushed with nitrogen, methanol is slowly added followed by the

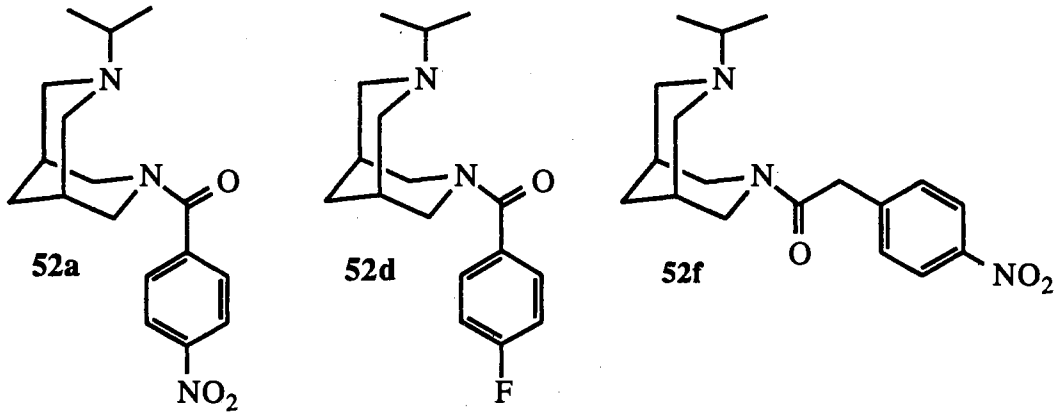
SCHEME III



addition of the amine and ammonium formate to give the best yields.

Amine **47c** was acylated using a modified Schotten-Baumann procedure[88] in which the amine was stirred at RT with an appropriate acid chloride in a biphasic reaction mixture of H_2CCl_2 and NaOH (10%) to give crude amides **39** and **50**. Flash chromatography using neutral alumina afforded the desired product **50** as an oil (82.4%) while amide **39** was isolated as a solid (83.1%) and did not require further purification. Amides **39** and **50** were then converted to their respective hydroperchlorates **51** (70.9%) and **42** (65.1%).

A key intermediate in the synthesis of amides **52a**, **52d**, and **52f** was amine **52j** (Scheme IV).[89] The preparation of these amides and derivatives thereof will be

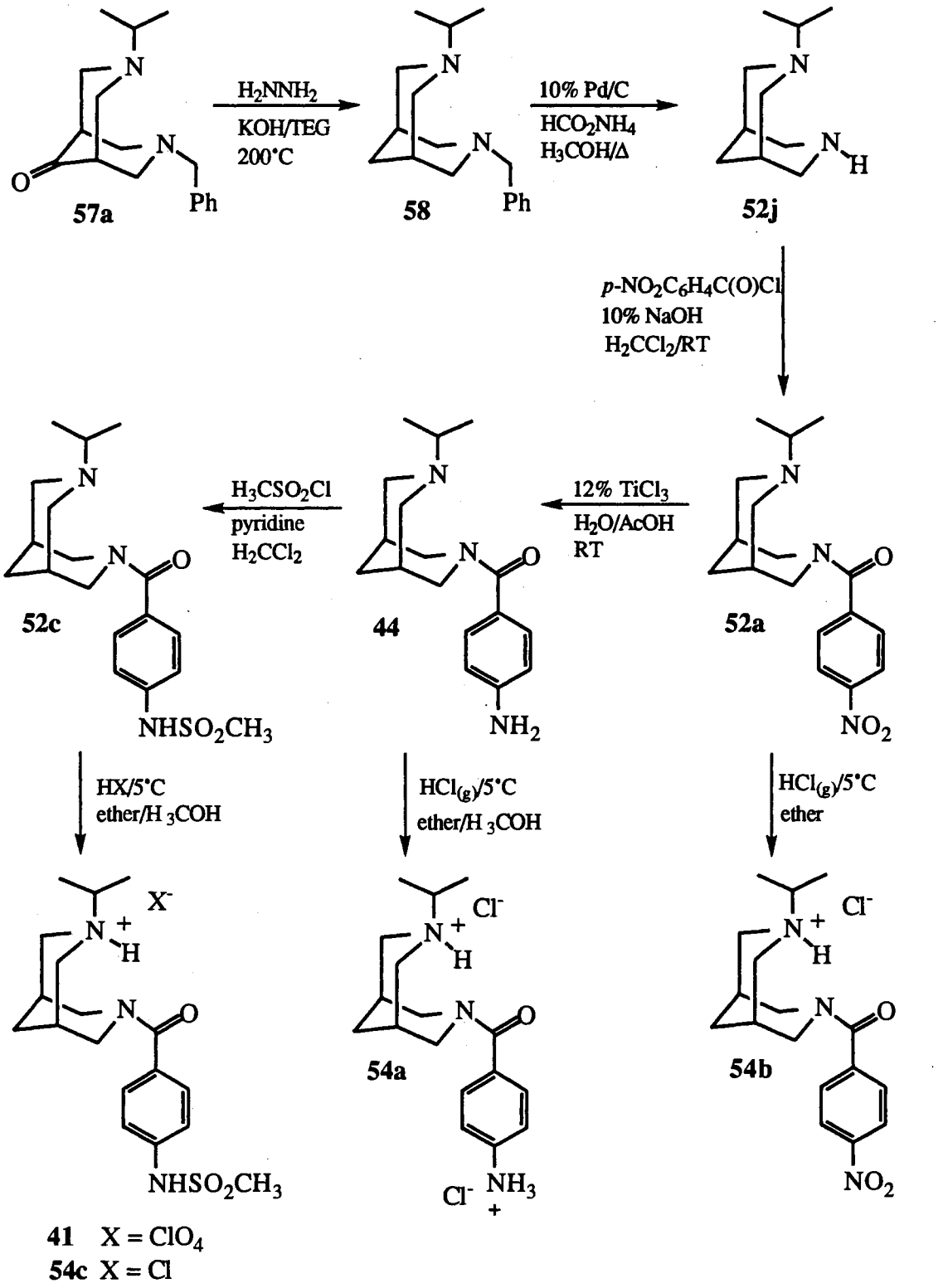


delineated in forthcoming schemes. Several derivatives prepared from these amides were found to possess good antiarrhythmic activity with indications of multiple class action.[29]

Ketone **57a** was reduced (Scheme IV) using standard Wolff-Kishner conditions to afford amine **58**. Debenzylation was effected using conditions described earlier to give secondary amine **52j** as an oil. Amine **52j** was acylated using Schotten-Baumann conditions (described in the preparation of amides **39** and **50**) to give amide **52a** (94.3%) as a light yellow solid. The NO_2 group in amide **52a** was reduced to a primary amine with $TiCl_3$ (12% solution in HCl) at RT in H_2O/acetic acid (1:1) and gave **44** (86.2%). $TiCl_3$ acts as a complexing agent in this redox reaction.[77] This reduction of aromatic NO_2 groups under mild conditions, although recently discovered,[77] is not fully understood. Formation of dihydrochloride **54a** from amide **44** was achieved following the procedure mentioned herein.

Hydrochloride **54b** was prepared directly from amide **52a** via the generation of $HCl_{(g)}$ by dropwise addition of sulfuric acid into a flask containing solid NaCl. The gas formed was passed through a $CaCl_2$ drying tube and subsequently into a chilled (~5°C)

SCHEME IV

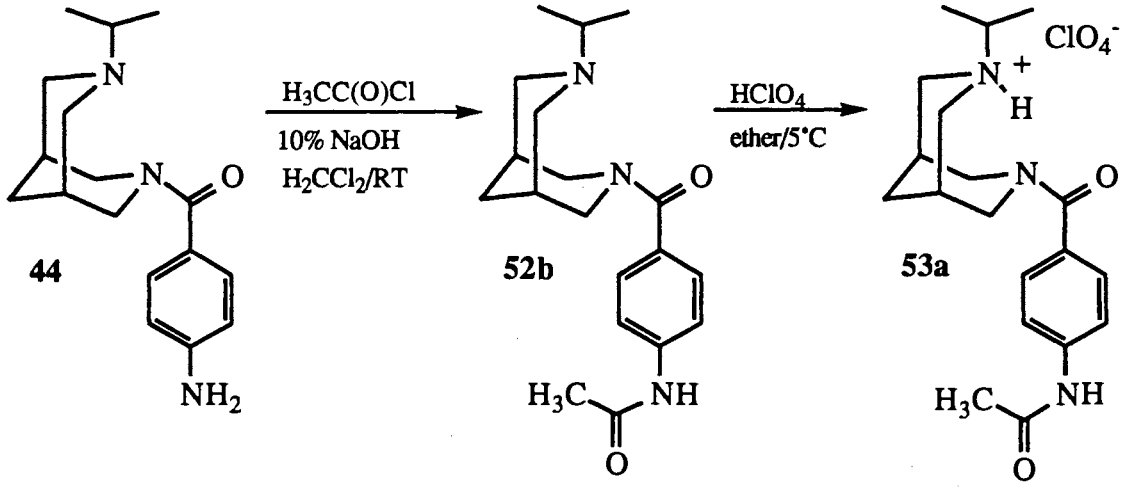


41 X = ClO_4
54c X = Cl

solution of amide **52a** to give salt **54b** (74.9%). This hydrochloride was found to be extremely soluble in water (>20 mg/ml) which might allow for better agent uptake when administered to a patient.

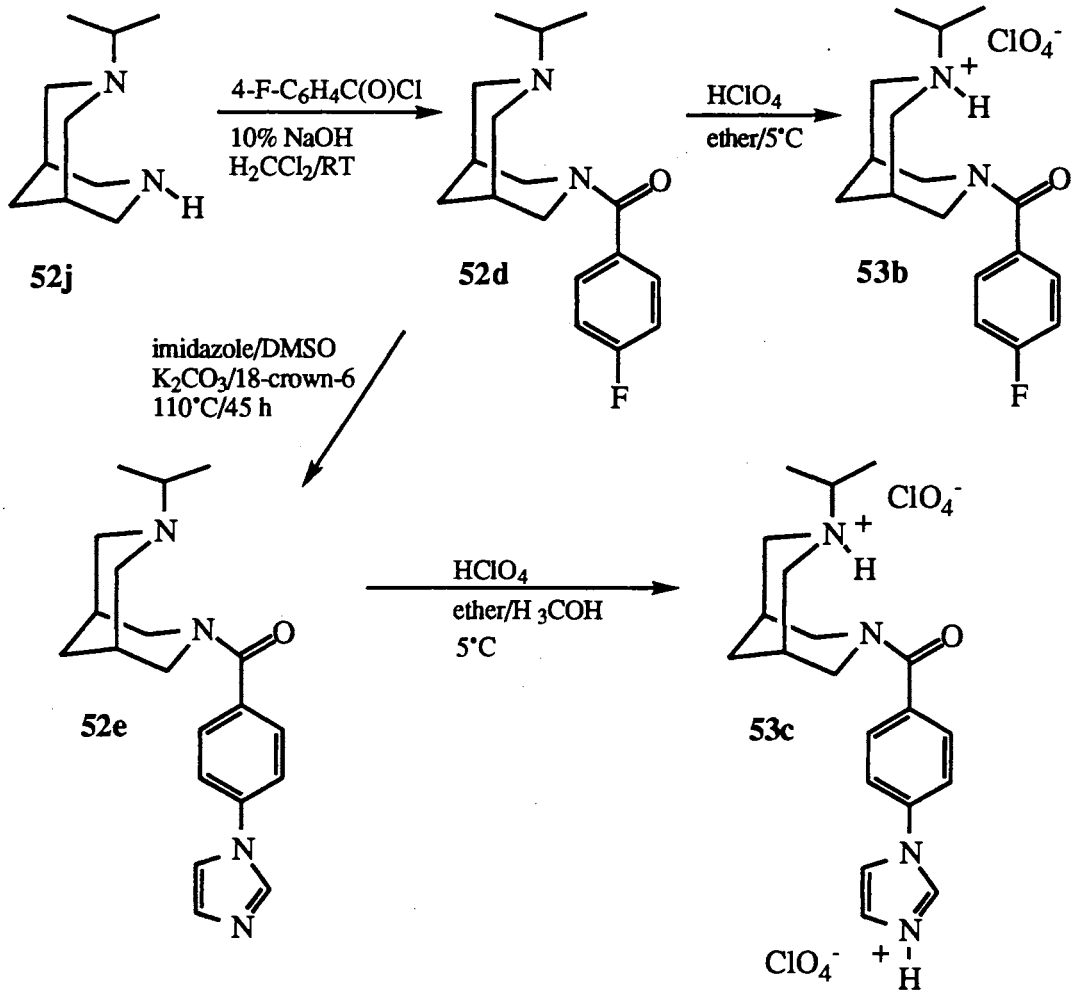
Conversion of amine **44** to sulfonamide **52c** [off white solid (90.6%)] occurred (Scheme IV) with methanesulfonyl chloride and pyridine in H_2CCl_2.[48] Amide **52c** was treated with $HClO_4$ or HCl in the usual manner to give hydroperchlorate **41** and hydrochloride **54c** in good yields, respectively. The sulfonamide group could be responsible for class III AAA.[22,55] In a similar manner, amide **44** was acylated (Scheme V) using acetyl chloride via Schotten-Baumann conditions to give amide **52b** as a crystalline solid which was spectroscopically identified and used without further purification to prepare hydroperchlorate **53a** .

SCHEME V



Introduction of the imidazole moiety into amide **52d** (Scheme VI) to give **52e** resulted in the an agent which possessed class Ib/III action Several synthetic approaches were attempted before obtaining the correct conditions in which the product formed and was isolable. Nucleophilic substitution on the aromatic ring of benzamide **52d** was achieved in the presence of imidazole, K_2CO_3, DMSO, and 18-crown-6 at a contant temperature (110°C) for 45 h. Amide **52e** was isolated as a light yellow solid (35.1%).

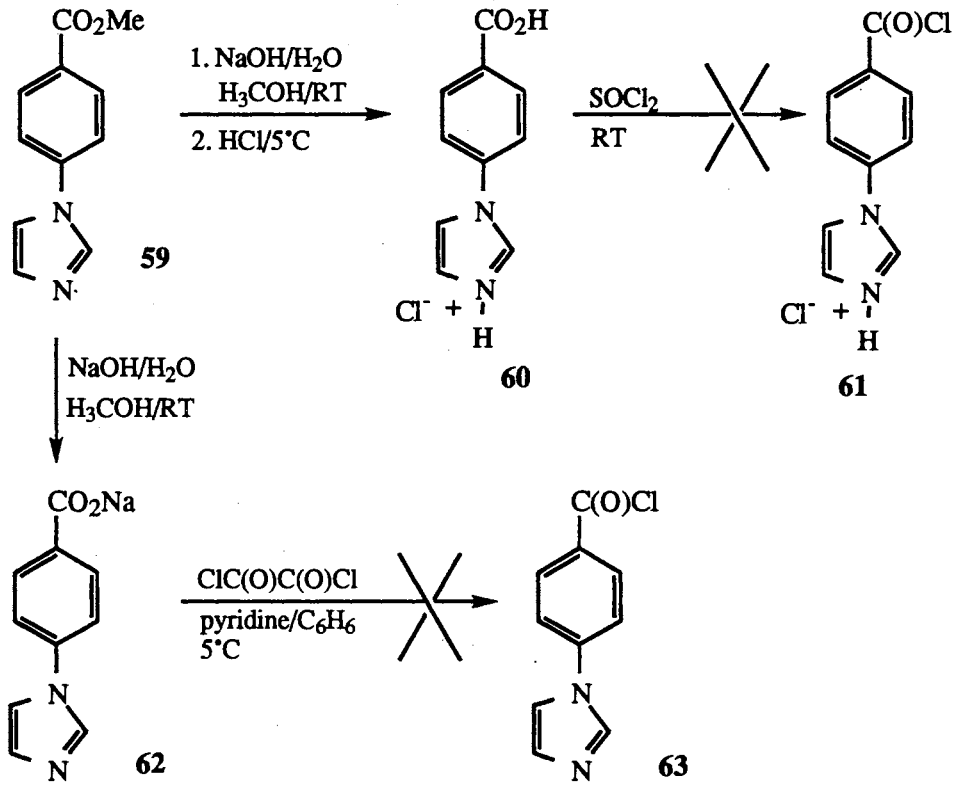
SCHEME VI



Dihydroperchlorate **53c** was prepared by the methods previously described. The modest yield of **52e** is likely due to the weak electron withdrawing ability of the amide functionality in **52d** which only mildly promotes diplacement of the F atom. Nucleophilic aromatic substitutions are known to proceed at a much higher yield with stronger electron withdrawing substituents.[5] It should be noted that in relation to other nucleophilic aromatic substitutions involving amides, the yield reported for **52e** is among the highest recorded for an amide.[5] For example, the reaction of 4-fluorobenzamide with piperidine gave 4-piperidinylbenzamide in a yield of only 30%.[5]

Since the reaction of **52d** resulted in a modest yield of **52e**, attempts were made to initiate a convergent synthesis to prepare **52e**. Saponification (Scheme VII) of ester **59**[49] using NaOH pellets in H_3COH/H_2O, followed by acidification with conc HCl, gave

SCHEME VII

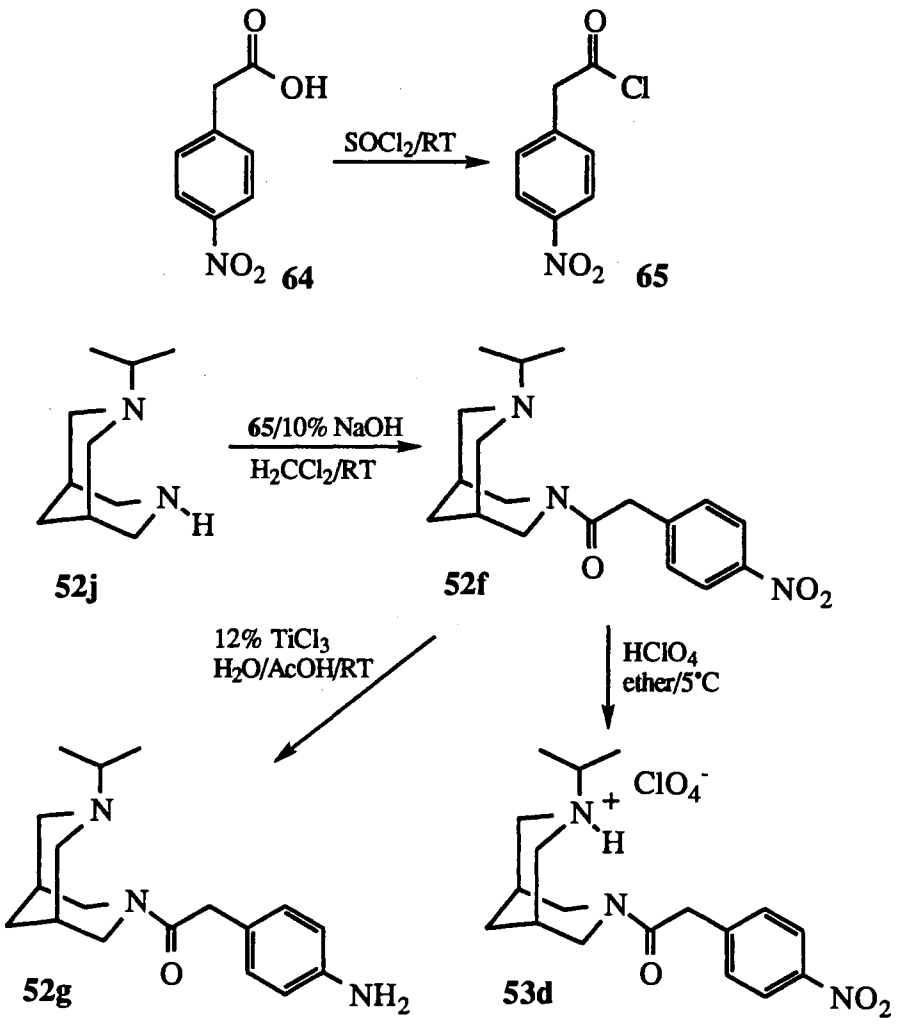


carboxylic acid **60**. Conversion of **60** to acid chloride **61** was attempted using $SOCl_2$ at RT, but, after workup, spectroscopic analysis indicated the presence of only starting material. The same reaction was attempted again by heating the reaction mixture for 4 h, but identical results were realized. Another method involved isolation of sodium salt **62** after saponification of ester **59**. Salt **62**, pyridine, and oxalyl chloride, were allowed to react at 5°C. Infrared analysis of the reaction mixture indicated the presence of only starting material **62**. The experiment was repeated and, after stirring the mixture with oxalyl chloride, another equal portion of oxalyl chloride was added. Workup yielded

only recovered **62**. One might suspect that the acid chloride may be self destructing to some degree by reacting with a nitrogen atom in the imidazole ring.

The synthesis of amide **52f** was realized (Scheme VIII) with a modified Schotten-Baumann procedure starting with amine **52j** and acid chloride **65** prepared from acid **64** with $SOCl_2$. Amide **52f** was converted to hydroperchlorate **53d** as shown and also to

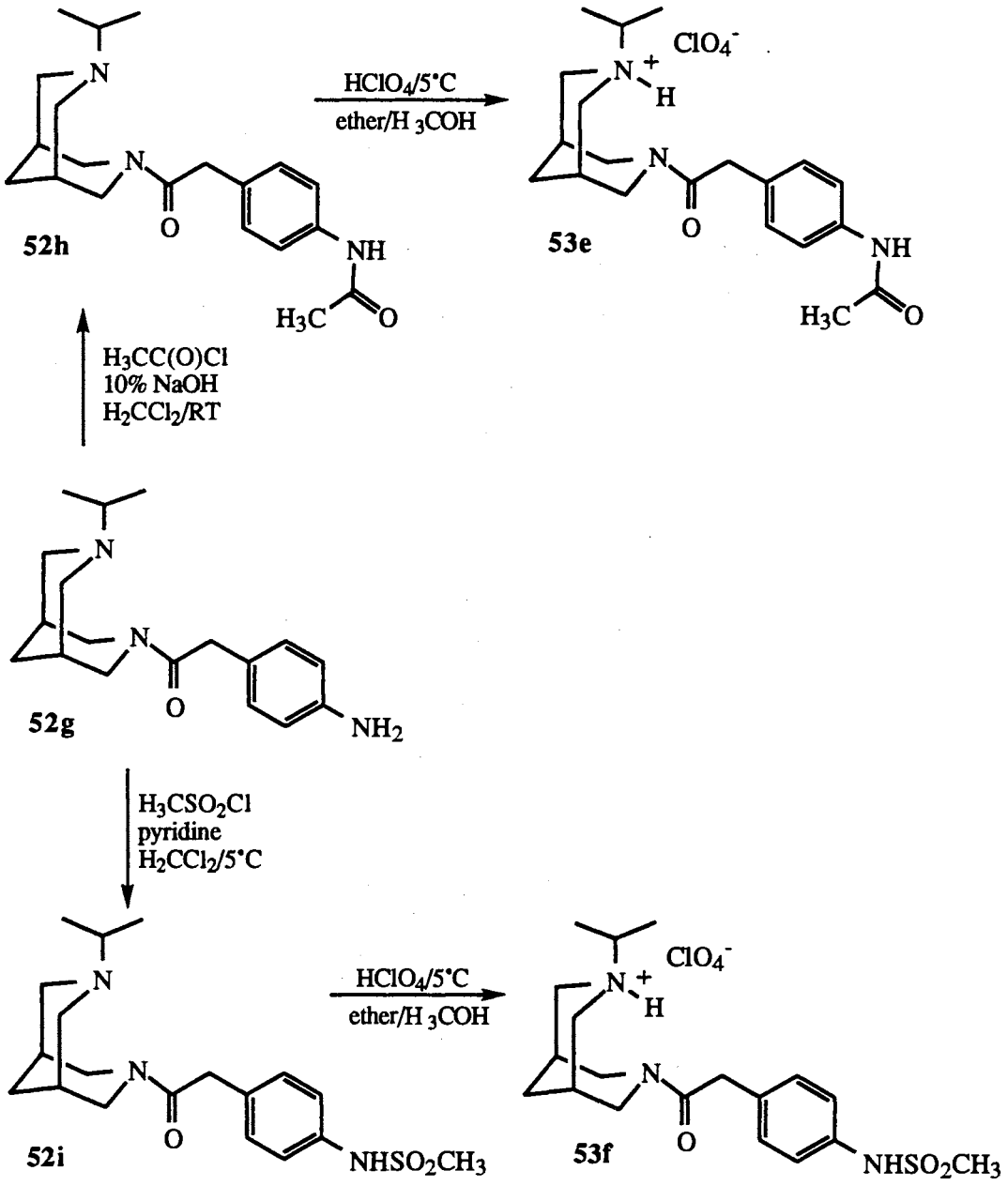
SCHEME VIII



p-aminobenzamide **52g** using $TiCl_3$ by methods described for the synthesis of amide **44**.

Compound **52g** was then converted (Scheme IX) to the *N*-acetyl derivative **52h** and sulfonamide **52i** as illustrated. Hydroperchlorates **53e** and **53f** were prepared in good

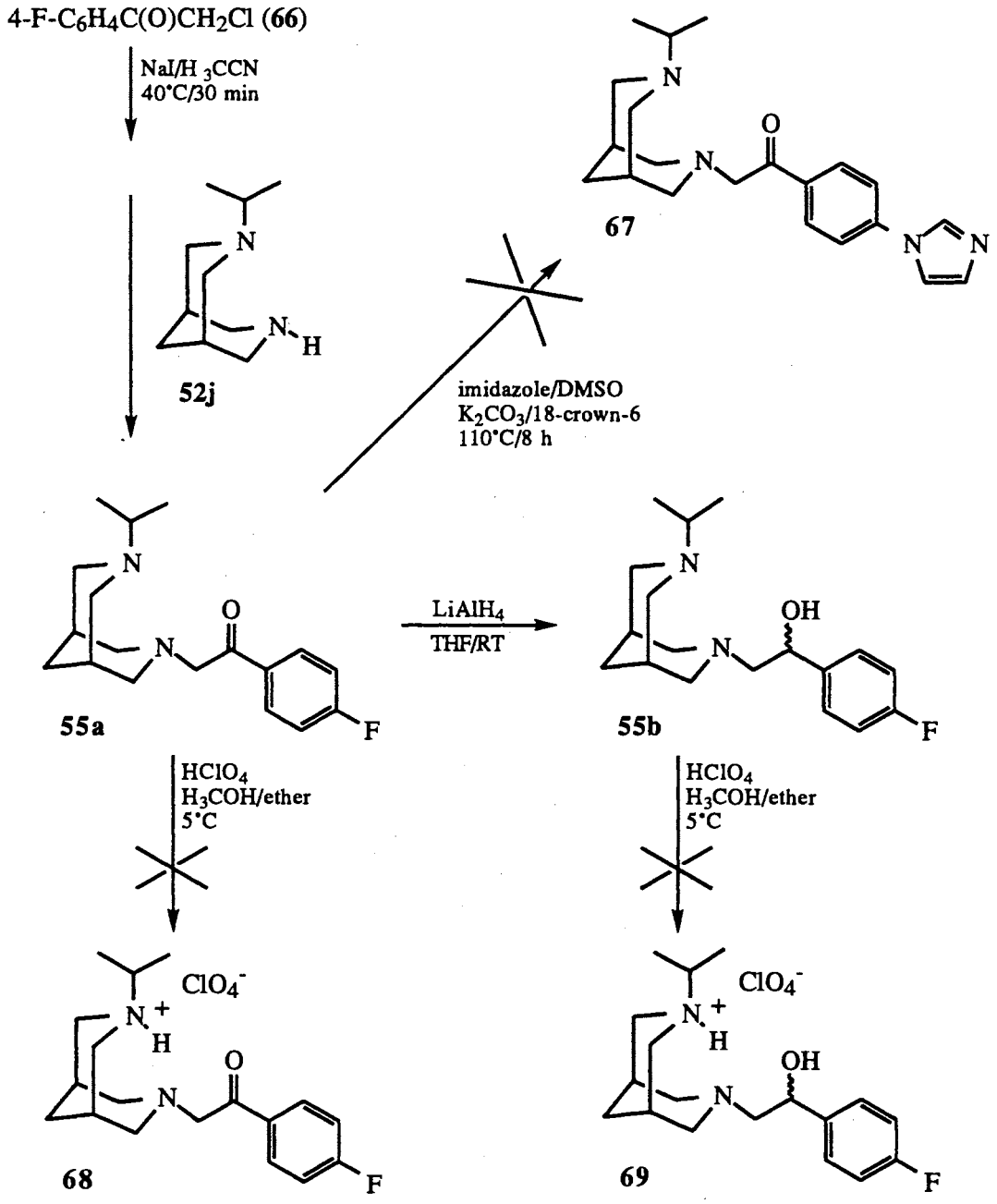
SCHEME IX



yields by the usual addition of $HClO_4$ to chilled (~5°C) solutions of the respective amides **52h** and **52i**.

Alkylation (Scheme X) of amine **52j** was more difficult than originally anticipated. Several methods were examined before conditions were discovered in which product

SCHEME X



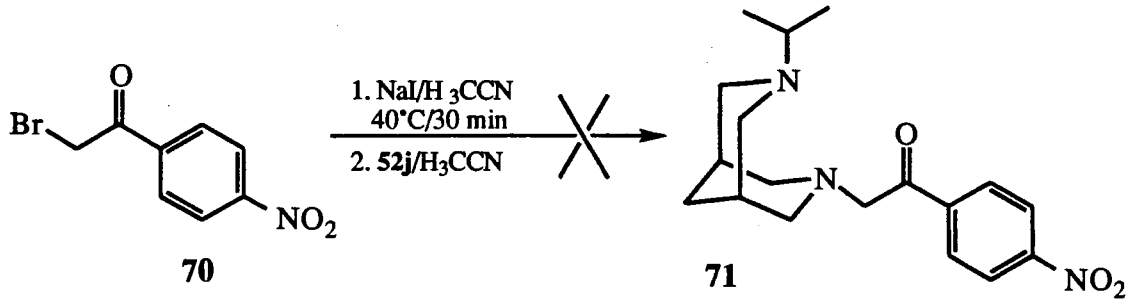
were discovered. Amine **52j** was added to a solution of α-chloroketone **66** and NaI in acetonitrile which gave, after an elaborate workup, α-aminoketone **55a** as an off-white solid (86.1%). Replacement of fluorine in **55a** by an imidazole moiety, as described in the conversion of **52d→52e**, was not successful. Amine **55a** in the presence of

imidazole, K_2CO_3, DMSO, and 18-crown-6 failed to react under a variety of conditions.

The carbonyl group in **55a** was expected to be more electron withdrawing than the amide function in **52d**.[5] The lack of reaction of **55a** is not completely understood at this time. One possible explanation is that K_2CO_3 at 110°C might be a strong enough base to extract a proton from the position alpha to the C=O group, thus significantly reducing the activation of the carbon bearing F and possibly initiating aldol type side reactions. The reaction of **55a** was carried out using a variety of conditions (various amounts of reagents) and using the large, hindered base 2,2,6,6-tetramethylpiperidine. This hindered amine was reasoned to be less effective in removing the hindered alpha protons adjacent to the carbonyl group in **55a**. Unfortunately, the results were unchanged, and starting material **55a** was recovered with no generation of ketone **67** which remains unknown.

Reduction of the ketone **55a** with $LiAlH_4$ in THF at RT gave racemic alcohol **55b** (Scheme X). Attempts to prepare salts of **68** and **69** resulted in the formation of oils from both systems, and solidification was not achieved. Spectral analysis suggests that the carbonyl group of **68** was converted to a 1,1-diol which may be the reason solidification did not occur although, interestingly, solid salts of 3,7-diheterabicyclo[3.3.1]nonan-9,9-diols are known.[8a] Compound **69** exhibited an O-H stretch in the IR indicating the presence of the alcohol moiety in the starting material. Although a protonated amine may be formed, but no solid material has been isolated to date.

Using identical conditions as in **66** + **52j** → **55a**, amine **52j**, NaI, and α-bromoketone **70** failed to react, with only starting material being recovered. As previously cited,

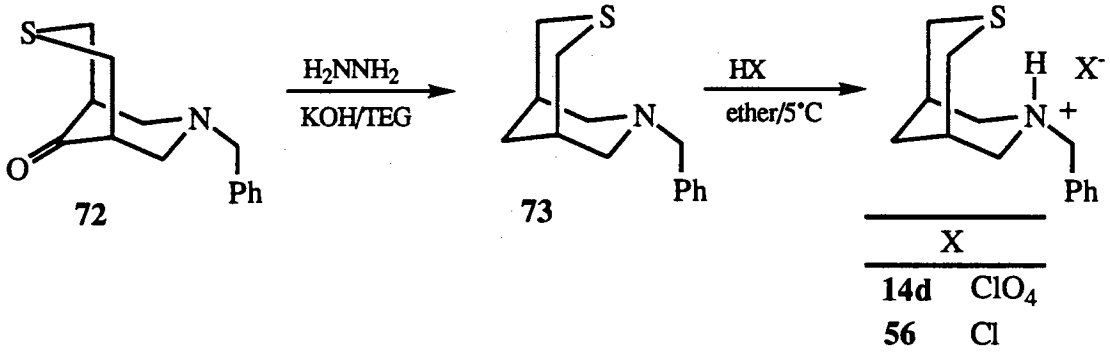


70 **71**

several different reaction regimes were attempted before the current procedure to prepare amine **55a** was discovered. These same conditions were examined with **52j** and **70** but did not lead to **71**. This reaction is still being investigated.

One of the most biologically active compounds our laboratory has reported[13] is hydroperchlorate **14d**. The synthesis of the intermediates[8a] are critical to the formation of related hydrochloride **56**. Reduction of ketone **72** (Scheme XI) using standard conditions afforded amine **73** in a good yield (88%). Hydroperchlorate **14d** was prepared by addition of $HClO_4$ to a chilled (~5°C) solution of amine **73**. Similar conditions were

SCHEME XI

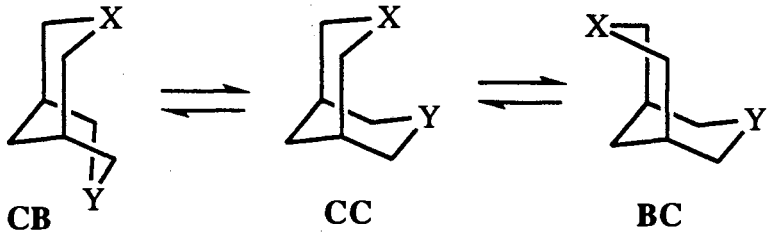


required for salt **56**, but the addition of $HCl_{(g)}$, generated as described for other hydrochlorides, gave the very water soluble **56**. Increased water solubility can enhance agent uptake and distribution when administered to patients for treatment of potentially lethal arrhythmias.

Several derivatives, namely **37**, **38**, **39**, **41-43**, **53c**, **54a**, **54b**, **54c**, and **56** have been screened by Dr. Scherlag of the VA Medical Center/OHSC in Oklahoma City for antiarrhythmic activity in dog models. Pharmacological studies are being performed by Dr. Sangiah and Chun-Lin Chen of the OSU College of Veterinary Medicine on compound **53c** which was found to be a very effective antiarrhythmic agent.[24] Detailed procedures for the aforementioned compounds are described in the Experimental Section.

NMR Properties of Amides in the 3,7-Diheterabicyclo[3.3.1]nonane Family

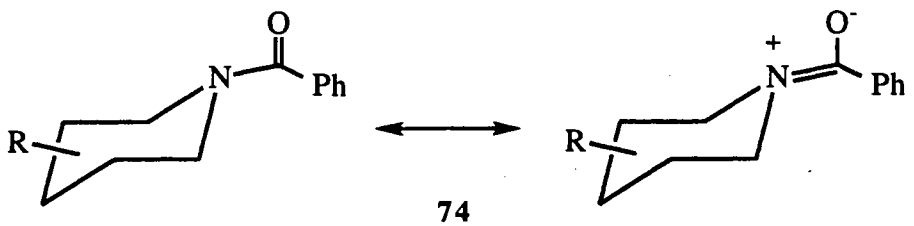
NMR spectroscopy and X-ray crystal analyses are crucial tools needed to identify the conformational preferences of 3,7-diheterabicycl[3.3.1]nonanes in solution and in the solid state, respectively. Analyses of this type can be useful in understanding biological properties and possibly an agent's mode of action. While X-ray crystal analysis gives a positive confirmation of the structure in the solid state, extrapolation to the major conformers present in solution must be exercised with caution. One study seemed to indicate that a BC⇄CB equilibrium[80] may operate in many DHBCN's in solution, but



DHBCN

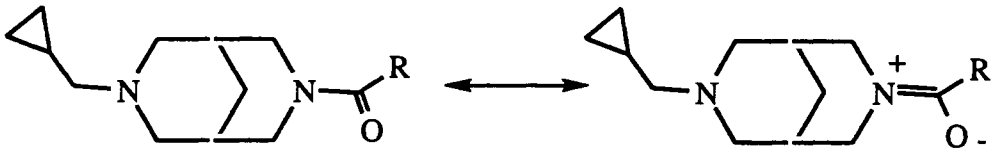
other work has indicated that these systems often take on one preferred conformation.[2,28] Definite proof for a particular DHBCN conformation in solution remains difficult. It is our intent to give a rational explanation concerning conformational preferences in solution for a series of related amides and their respective hydroperchlorates. These findings are supported by NMR data and help to substantiate the conclusions from previous work.[2,28,80]

The ^{1}H and ^{13}C NMR spectra on a series of amides synthesized in the current work were found to have several unique features which suggest certain conformational properties. Simple model amides, such as *N*-benzoylated piperidines **74**, apparently prefer flattened chair conformations in solution as assessed by analysis of variable temperature ^{1}H NMR[37] and ^{13}C NMR[33] data. It is possible that the amides herein may



74

exhibit effects similar to those seen in these simple systems. Conformational preferences may be due, in part, to a minimum energy arrangement in which of the p orbital of the carbonyl π system and the lone pair on nitrogen overlap (atoms attached to the amide system will assume a nearly planar arrangement). Resonance forms of this familiar phenomena are illustrated for **39**.



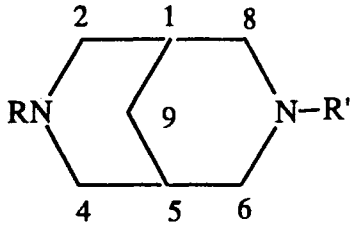
39 R = 4-Cl-C_6H_4

Rotational barriers in related benzamide systems have been reported to be approximately 14-16 kcal/mol via ^1H and ^{13}C NMR experiments.[33] Amides **39, 44, 50, 52a-i** demonstrate this effect in that all the carbon signals in the ^{13}C NMR spectra are nonequivalent (thus the energy barrier to rotation of the amides is not reached at RT). The NMR assignments (Tables XV, XVI) are based on related systems and further supported by COSY (Figure 2) and HETCOR 2D (Figure 3) NMR analysis of **39**.

Spectral analysis using 2D NMR techniques was found to be helpful in making structural assignments for **39**. Correlations between the carbons and hydrogens in **39** where determined in an easy manner using a HETCOR 2D experiment (Figure 3). Amide **39** displayed some complicated long range splitting patterns which where dissected using a COSY experiment (Figure 2)

TABLE XV

^{1}H NMR SPECTRAL DATA FOR AMIDES **39, 44, 50, 52 a-e**[a] (δ VALUES)



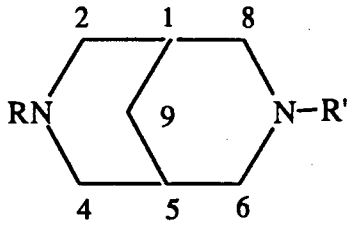
	R	R'
39	$C(O)C_6H_4$-4-Cl	CH_2-cPr
44	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
50	C(O)Ph	CH_2-cPr
52a	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$
52b	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
52c	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
52d	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
52e	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$

Cpd	H(1)	H(5)	H(9)	H(2,4,6,8)	$CH(CH_3)_2$	CH_3	NCH_2-cPr	cPr-*CH*	cPr-*CH2*
39	2.02	1.73	1.73	2.24, 2.96, 3.03, 3.28, 3.75, 4.83	-	-	2.02, 2.24	0.91	0.12, 0.54
44	1.91	1.67	1.67	2.41, 2.72, 3.02, 3.31, 3.83, 4.70	2.59	0.98	-	-	-
50	1.98	1.74	1.74	2.23, 2.94, 3.01, 3.28, 3.78, 4.79	-	-	1.98, 2.23	0.92	0.49, 0.92
52a	1.61	1.34	1.34	2.04-2.32, 2.67, 2.94, 3.20, 3.39,	2.32	0.56, 0.69	-	-	-
52b	1.96	1.96	1.74	2.42, 2.48, 2.71, 3.04, 3.30, 3.79, 4.76	2.56	0.94, 1.03	-	-	-
52c	1.98	1.69	1.79	2.42, 2.51, 2.74, 3.03, 3.32, 3.78, 4.76	2.60	0.97, 1.08	-	-	-
52d	1.95	1.71	1.71	2.41-2.72, 3.03, 3.31, 3.72, 4.47	2.71	0.96, 1.07	-	-	-
52e	1.81	1.81	1.68	2.45, 2.57, 2.77, 3.09, 3.38, 3.76, 4.79	2.63	0.96-1.14	-	-	-

[a]$DCCl_3$ solutions referenced to TMS (tetramethylsilane) at 0 ppm.

TABLE XVI

^{13}C NMR SPECTRAL DATA FOR AMIDES **39, 44, 50, 52 a-e**[a] (PPM)



	R	R'
39	$C(O)C_6H_4$-4-Cl	CH_2-cPr
44	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
50	C(O)Ph	CH_2-cPr
52a	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$
52b	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
52c	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
52d	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
52e	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$

Cpd	C(1)	C(5)	C(9)	C(2)	C(4,6,8)	$CH(CH_3)_2$	CH_3	NCH_2-cPr	cPr-CH	cPr-CH_2	NC=O
39	29.01	29.41	32.10	46.59	52.16, 58.10, 58.38	-	-	64.25	8.29	3.21, 4.43	169.06
44	29.15	29.79	32.25	46.61	52.59, 54.22	54.22	16.81, 18.79	-	-	-	170.47
50	28.64	29.01	31.72	46.02	51.74, 57.71, 57.98	-	-	63.84	7.95	2.85, 4.11	169.68
52a	28.81	29.57	32.04	46.55	51.79, 52.31, 54.85	54.26	15.89, 19.46	-	-	-	167.58
52b	29.05	29.65	32.20	46.70	52.24, 52.85, 54.63	54.24	16.29, 19.24	-	-	-	170.19
52c	28.89	29.55	32.05	46.76	52.11, 52.52, 54.54	54.19	16.26, 19.16	-	-	-	169.63
52d	28.97	29.69	32.16	46.59	52.12, 52.49, 54.65	54.65	16.26, 19.18	-	-	-	169.07
52e	29.03	29.78	32.26	46.72	52.15, 52.61, 54.82	54.38	16.33, 19.41	-	-	-	168.80

[a]$DCCl_3$ solution reference to TMS (tetramethylsilane) at 0 ppm.

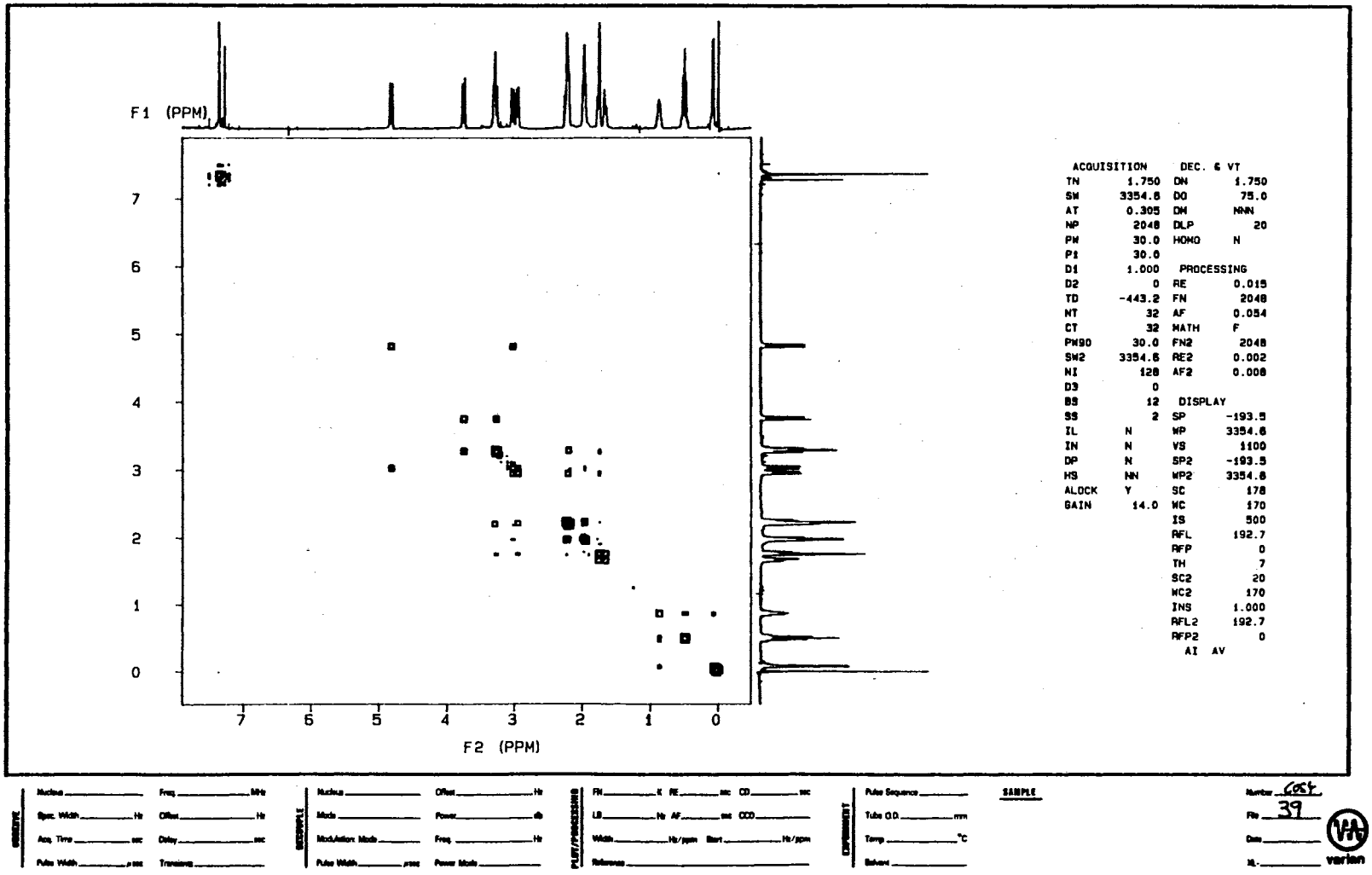


Figure 2. COSY Spectrum of Amide **39**

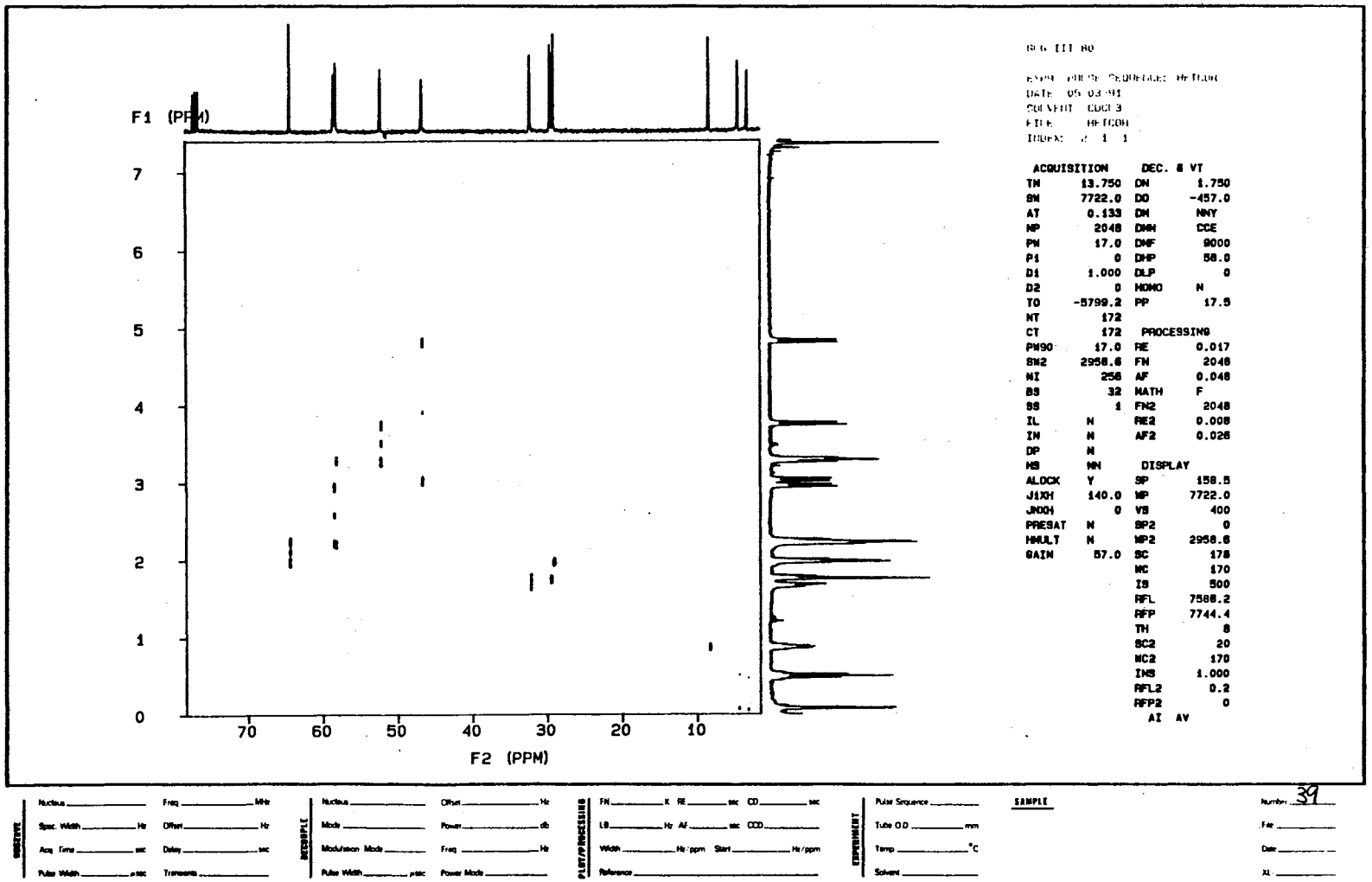


Figure 3. HETCOR Spectrum of Amide **39**

For example, the axial and equatorial protons in the 2-, 4-, 6-, and 8-positions of the bicyclic ring display a doublet of a doublet as a splitting pattern. Geminal coupling created the large doublet ($^2J_{H-H}$ = 13.1 Hz) and this doublet was split into doublets by virtue of vicinal coupling ($^3J_{H-H}$ = 3.8 Hz). Vicinal coupling is believed to be the reason for the observed complexed splitting patterns.

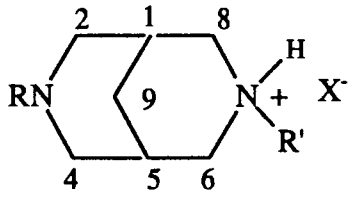
In contrast, the NMR spectra of the amide *salts* were found to be completely different in that the nonequivalency seen in the unprotonated amides was *not* observed in the protonated species. Carbons at the 2-, 4-, 6-, and 8-positions of the bicyclic ring and the isopropyl methyl groups (**41, 53a,b,c,d,e,f, 54a,b,c**) diplayed three very broad singlets in the ^{13}C NMR spectra at RT. The ^1H NMR (Tables XVII) and ^{13}C NMR (Tables XVIII) assignments illustrate the observed differences in the salts as compared to the unprotonated amides.

To assess the conformational changes, a variable temperature study of the ^{13}C NMR resonances of selected *amide salts* **51**, **53b**, and **53d** was performed within the temperature range of -35 to 60°C, and the results have been tabulated in Table XIX. At -35°C, the spectra became very complex in that all of the carbon signals became nonequivalent (same effect seen in the *unprotonated forms at RT*) while at 60°C the broad ^{13}C signals seen at RT became relatively sharp singlets. These results imply that spectra of the amide salts reflect an average conformation at 60°C while a preferred conformation is observed at -35°C. Thus the barrier to amide rotation is much lower in the amide salts compared to that in the unprotonated amides.

An explanation of this effect can be viewed by analysis of previous work in this field.[6,8] An X-ray diffraction analysis of hydroperchlorate **14d** revealed a chair-chair form, as was true for many salts of 3,7-diheterabicyclo[3.3.1]nonanes due to internal hydrogen bonding between the proton and the lone pair of electrons on the other heteroatom.[6,8] However, NMR studies could not eliminate the presence of a small

TABLE XVII

^{1}H NMR SPECTRAL DATA FOR HYDROPERCHLORATES **41, 42, 53a-c, 54a, 54b**[a] (δ VALUES)



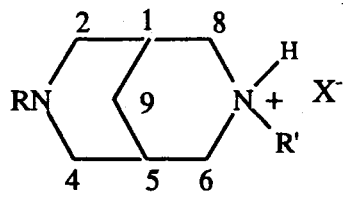
	R	R'
41	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
42	C(O)Ph	CH_2-cPr
51	$C(O)C_6H_4$-4-Cl	CH_2-cPr
53a	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
53b	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
53c	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$
54a	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
54b	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$

Cpd	H(1)	H(5)	H(9)	H(2,4,6,8)	Ar-*H*	C*H*$(CH_3)_2$	C*H*$_3$	NC*H*$_2$-cPr	cPr-C*H*	cPr-C*H*$_2$	X
41[b]	2.24	2.24	1.87	3.18-3.55	7.24, 7.37	3.18-3.55	1.32	-	-	-	ClO_4
42	2.24	2.24	1.83	3.21, 3.71, 4.08	7.41	-	-	2.98	1.19	0.52, 0.81	ClO_4
51	2.33	2.33	1.85	3.29, 3.74, 4.09	7.36, 7.48	-	-	3.03	1.18	0.51, 0.82	ClO_4
53a	2.33	2.33	1.82	3.16, 3.29, 4.10	7.22, 7.57	3.55	1.38	-	-	-	ClO_4
53b	2.29	2.29	1.81	3.34, 3.52	7.17, 7.38	3.34	1.38	-	-	-	ClO_4
53c[b]	3.03	3.03	2.34	3.23-3.97	7.66, 7.96	3.23-3.97	1.33	-	-	-	ClO_4
54a[c]	2.49	2.49	2.03	3.40-3.67	7.62	3.40-3.67	1.45	-	-	-	Cl
54b[c]	2.52	2.52	2.03	3.39-3.67	7.71, 8.36	3.39-3.67	1.44	-	-	-	Cl

[a]Samples were run in D_3CCN (unless otherwise noted) referenced to TMS (tetramethylsilane) at 0 ppm.
[b]DMSO-d_6 solution.
[c]D_2O solution.

TABLE XVIII

^{13}C NMR SPECTRAL DATA HYDROPERCHLORATES **41, 42, 53a-c, 54a, 54b**[a] (δ VALUES)



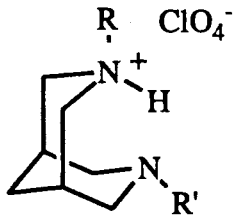
	R	R'
41	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
42	C(O)Ph	CH_2-cPr
51	$C(O)C_6H_4$-4-Cl	CH_2-cPr
53a	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
53b	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
53c	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$
54a	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
54b	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$

Cpd	C(1)	C(5)	C(9)	C(2,4,6,8)	$CH(CH_3)_2$	CH_3	NCH_2-cPr	cPr-CH	cPr-CH_2	NC=O	X
41[b]	27.59	27.59	27.59	59.53	59.53	26.48	-	-	-	172.62	ClO_4
42	26.45	26.45	27.76	62.56	-	-	62.56	5.27	5.27	172.69	ClO_4
51	27.89	27.89	29.05	57.42, 63.89	-	-	64.08	6.40	4.94	173.85	ClO_4
53a	28.01	28.01	29.22	50.42, 53.92	61.14	16.90	-	-	-	175.02	ClO_4
53b	27.89	27.89	28.99	50.34, 53.52	60.96	16.72	-	-	-	174.13	ClO_4
53c[b]	26.42	26.42	27.36	59.64	59.64	-	-	-	-	171.49	ClO_4
54a[c]	29.84	29.84	30.14	52.19, 55.26	63.65	18.83	-	-	-	177.42	Cl
54b[c]	29.36	29.36	29.36	49.42, 54.01	63.38	19.82	-	-	-	175.77	Cl

[a]Samples were run in D_3CCN (unless otherwise noted) referenced to TMS (tetramethylsilane) at 0 ppm.
[b]DMSO-d_6 solution.
[c]D_2O solution.

TABLE XIX

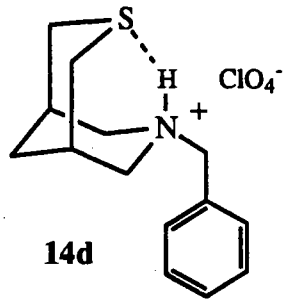
VARIABLE TEMPERATURE ^{13}C NMR SPECTRAL DATA OF HYDROPERCHLORATES **51, 53b, 53d**[a] (PPM)



	R	R'
51	CH_2-cPr	$C(O)C_6H_4$-4-Cl
53b	$CH(CH_3)_2$	$C(O)C_6H_4$-4-F
53d	$CH(CH_3)_2$	$C(O)CH_2C_6H_4$-4-NO_2

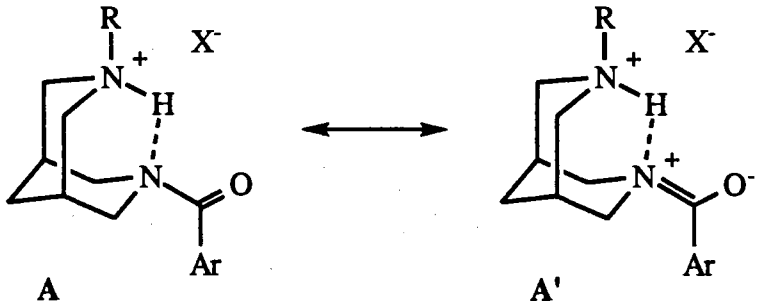
Cpd	Temp	C(1)	C(5)	C(9)	C(2)	C(4,6,8)	$\underline{C}H(\underline{C}H_3)_2$	$NC\underline{C}-\underline{C}(\underline{C})\underline{C}$	NC=O
51	60°C	28.34	28.34	29.38	50.39	50.39, 58.01	-	5.03, 6.63	173.97
	25°C	28.01	28.01	29.16	bs, 50.00	(bs, 50.00, 57.47)	-	(bs, 4.77), 6.48	173.88
	-35°C	27.27	27.58	28.75	46.98	51.99, 55.45, 58.15	-	3.24, 5.75, 6.24, 63.62	173.74
53b	60°C	28.36	28.36	29.38	50.59	50.59, 54.27	17.59, 61.52	-	174.29
	25°C	27.89	27.89	28.99	bs, 50.20	(bs, 50.20, 53.30)	(bs, 16.72), 60.96	-	174.13
	-35°C	27.69	27.69	28.88	47.53	50.04, 52.28, 55.99	14.45, 18.86, 60.79	-	173.98
53d	60°C	28.19	28.19	28.90	48.97	48.97, 54.34	17.08, 61.39	-	174.13
	25°C	27.84	27.84	28.58	bs, 49.20	(bs, 49.20, 53.90)	(bs, 16.77), 61.01	-	174.00
	-35°C	25.87	26.11	26.74	45.49	48.00, 50.67, 52.72	14.31, 15.82, 59.11	-	173.82

[a]D_3CCN solution referenced to TMS (tetramethylsilane) at 0 ppm.



14d

concentration of a CB form in solution for **14d**. Obviously, a CC conformation for the amides will induce hydrogen bonding between an N-H proton and the lone pair of electrons on the nitrogen atom of the amide function. This may result in the *loss of double bond character* of the amide N-C(O) bond and thus lead to *increased rotation* at RT. This implies that of the resonance forms A and A', A' makes a smaller contribution

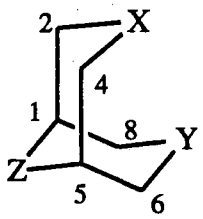


to the hybrid in the amide-salts than in the simple amides. Variable temperature studies showed that at higher temperatures the carbonyl is more *deshielded* than at lower temperatures (carbonyl assumes more ketone characteristics at higher temperatures) in the ^{13}C NMR.

The ^{15}N NMR spectral analysis (Table XX) provided information regarding the location of protonation in hydroperchlorate **37**. Assignments were based upon simple piperidine[43] systems and previous work from our laboratory. NMR spectra of **39**, **57b**, and salts **41** and **51** were helpful in providing insight into the RT conformer. As mentioned earlier, it was thought that the amide salts existed predominantly in the CC

TABLE XX

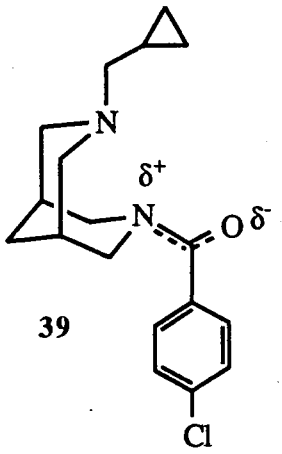
^{15}N NMR SPECTRAL DATA (PPM)[a] of **37, 39, 42, 46b, 51, 52d**



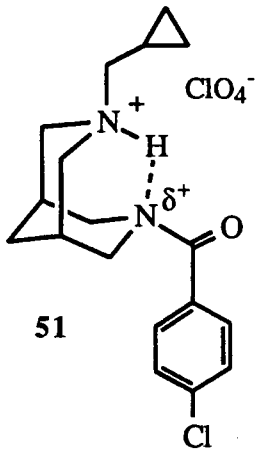
Cpd	X	Y	Z	N(3)	N(7)
37[c]	$\overset{+}{N}(H)CH_2$-cPr[d]	NCH_2Ph	CH_2	55.18	49.22
39[b]	$NC(O)C_6H_4$-4-Cl	NCH_2-cPr	CH_2	119.74	40.55
42[c]	NC(O)Ph	$\overset{+}{N}(H)CH_2$-cPr[d]	CH_2	108.49	50.50
46b[b]	NCH_2-cPr	NCH_2Ph	C(O)	37.74	36.17
51[c]	$NC(O)C_6H_4$-4-Cl	$\overset{+}{N}(H)CH_2$-cPr[d]	CH_2	109.19	49.82
52d[b]	$NC(O)C_6H_4$-4-F	$NCH(CH_3)_2$	CH_2	119.65	40.78

[a]All spectra were obtained at RT using an 8 *M* $^{15}NH_4NO_3$ external standard (19.73 ppm) which was cross-referenced to liquid NH_3 at 0 ppm (reference 43).
[b]$DCCl_3$.
[c]DMSO-d_6.
[d]Counterion is ClO_4^-.

conformation in solution at RT. As seen in Table XX, amide **39** had an N(3) signal at 119.74 ppm while the corresponding salt **51** displayed an N(3) signal at 109.19 ppm that was more *shielded.* This is an opposite effect to that seen in salts of DHBCN containing two tertiary nitrogen atoms. For example, the ^{15}N spectrum of ketone **46b** has an N(3) signal (37.74 ppm) while N(7) is located at 36.17 ppm. Reduction of **46b** and conversion of the intermediate diamine to salt **37** followed. Salt **37** has two nitrogen resonances



39

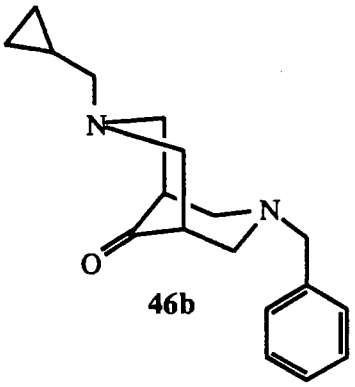


51

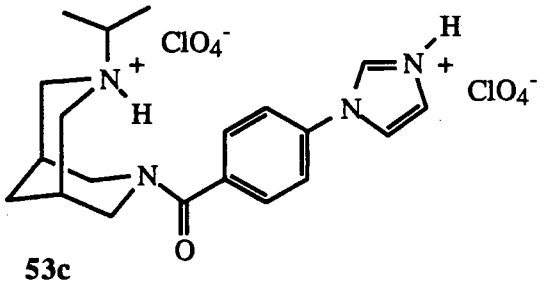
highly *deshielded* [N(3) = 55.18 and N(7) = 49.22 ppm] compared to those in **46b**. Salts like **37** often exhibit strong deshielding of the nitrogen atom possessing the proton while the other nitrogen atom is mildly deshielded probably because of hydrogen bonding. Shielding of the nitrogen atom [N(3)] of the amide linkage in salt **51,** as compared to the N(3) nitrogen of the amide linkage in **39**, can be partially explained by the intensity of the electron deficit existing on the N(3) nitrogen atoms. Hydrogen bonding with the lone pair on nitrogen has two effects on the system: 1) the amount of double bond character of the C-N bond is significantly reduced and thus the amount of C(O)-N bond rotation should increase, and 2) since the lone pair is involved in hydrogen bonding, the partial positive charge on the amide nitrogen in **51** will be diminished in comparison to the partial positive charge in the unprotonated amide **39**.

Conformational preferences of our 3,7-diheterabicyclo[3.3.1]nonanes in solution are

difficult to establish absolutely, but an accumulation of data from various spectral techniques support the assignment of the structures illustrated in the thesis.[6,8] Currently, compounds **46b** and **53c** have been submitted for X-ray analysis which should establish the most stable conformation in the solid state. Preliminary analysis of the X-ray diffraction data indicates that **46b** is a BC system while the salt **53c** is a CC form.



46b



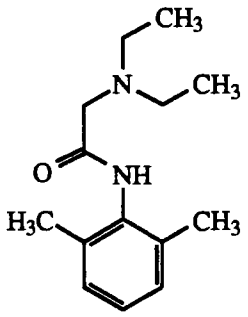
53c

Achieving a better understanding of the conformational properties of DHBCN may help explain some of the observed biological actions.

Antiarrhythmic Activity

The antiarrhythmic properties of **14b, 14d, 37-39, 41-43, 53c, 54a, 54b, 54c**, and **56** have been evaluated by Dr. Scherlag at the VAMC/OHSC in Oklahoma City, Oklahoma. The compounds were studied in fifteen anesthetized mongrel dogs which were examined after the occlusion of the left anterior descending coronary artery and after the dogs were allowed to recover for 24-96 h.[8,24,58] Ths occlusion results in a transmural myocardial infarction of the heart in which accelerated idioventricular rhythms are observed interdispersed with the beats of the normal sinus rhythm. Electrical output of the heart is monitored using a 12-lead electrocardiogram (ECG) to ascertain the presence and the extent of myocardial infarction. Induction of sustained ventricular tachycardia (SVT is defined as a series of ventricular beats which are usually uniform at a rate of 250

beats/min or more) was initiated using programmed electrical stimulation (PES) which followed with the test agents at doses of 3 and 6 mg/kg and which were administered intravenously (i.v.). The agent's ability to terminate SVT or to prevent the induction of SVT was measured in all experiments. Lidocaine (**7**) was used as the standard for comparison purposes since it is currently the agent of choice in the treatment of SVT.[46]



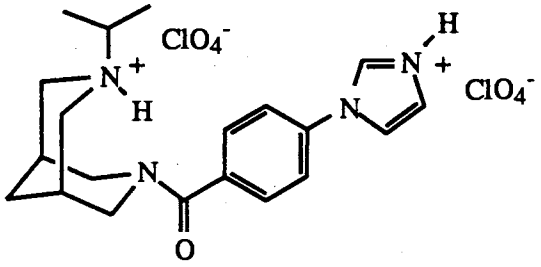
Lidocaine
7

Several parameters were measured in the experiment to determine the different class actions of each agent. These parameters include MBP (mean blood pressure), HR (heart rate), AH interval (Atrial His-bundles; measured conduction time), HV interval (His to ventricular activation; measures sodium channel action), QT interval (time to complete the process of depolarization and repolarization), VERP (ventricular effective refractory period; time elapsed to complete the QRS complex of the ECG), and the ability of each agent to prevent sustained ventricular tachycardias. Prolongation of the VERP, AH, HV, and the QT intervals suggests that a particular agent possesses some class III antiarrhythmic activity. This does not mean that all of these parameters must be prolonged in order to obtain such action but such was found with many agents claiming class III activity.[12,17,22,23,32,38,45,49,55] In the experiments performed, lidocaine (**7**) was found to exhibit no class III action and only reduced the rate of sustained ventricular tachycardia (SVT). Lidocaine is known to possess class Ib action.[42]

Several of the DHBCN agents tested were shown to possess excellent antiarrhythmic

activity in dog models. Effects on the class III parameters varied between agents and nearly all of which abolished the VT at the 3 and 6 mg/kg dosage levels. Specifically, four compounds (**38, 39, 42, 53c**) exhibited outstanding activity in the animal models.

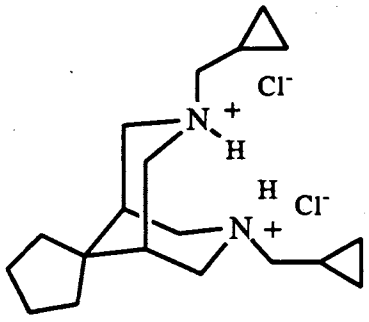
The best compound synthesized to date in our laboratory is dihydroperchlorate **53c**. This agent slightly reduced the MBP but the effect was only short lasting. Salt **53c** also



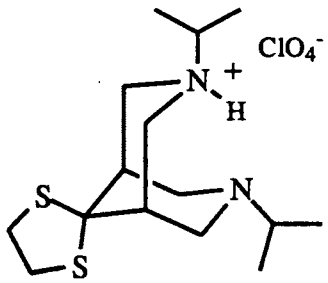
53c (GLG-V-13)

significantly reduced the HR and prolonged the VERP, AH, HV, and the QT intervals.[29] From the accumulated data (Table XXI), it was concluded that this agent possessed class Ib/III AAA. Presently, **53c** is undergoing detailed electrophysiological studies by Dr. Papp in Hungary at the Szent-Gyorgyi University Medical School. A three generation toxicity study on mice is currently underway with the research being directed by Dr. Sangiah in the Physiological Science Department of the Oklahoma State College of Veterinary Medicine. Results of both studies are pending.

Tedisamil (**29**) is a known K^+ current blocker,[7] and GLG IV-57 (**38**) shows some structural similarities, but it could *not* be considered a tedisamil analogue due to the



29 (Tedisamil)



38 (GLG-IV-57)

TABLE XXI

ANTIARRHYTHMIC PROPERTIES[a] OF THE MOST ACTIVE DHBCN **14b, 38, 39, 42,** AND **53c**

Cpd	HR[b]		MBP[c]		QT interval[d]		AH interval[e]		HV interval[f]		VERP[g]	
	pre[h]	post[i]	pre	post	pre	post	pre	post	pre	post	pre	post
7 (lidocaine)	NE[j]	NE	105	84	NE	NE	NE	NE	NE	NE	NE	NE
14b (GLG-III-93)	150	110	110	55	NM[k]	NM	64	70	NE	NE	170	230
38 (GLG-IV-57)	154	105	61	76	136	170	56	75	30	40	140	180
39 (GLG-III-70)	125	105	88	98	215	250	60	68	NE	NE	170	220
42 (GLG-III-96)	120	111	92	83	NE	NE	65	70	NE	NE	170	190
53c (GLG-V-13)	152	110	94	84	222	288	57	66	30	37	142	187

[a]Antiarrhythmic properties are compared to lidocaine using doses (3 mg/kg) in which SVT was non-inducible in the DHBCN system while lidocaine only reduced the rate of the VT.

[b]HR = Heart rate (beats/min).

[c]MBP = Mean blood pressure (mm Hg).

[d]QT interval = Time (msec) required for the cell to undergo depolarization and repolarization.

[e]AH interval = (msec) measures conduction time.

[f]HV interval = (msec) measures sodium channel action.

[g]VERP = (msec) elapsed time to complete the QRS complex of ECG.

[h]Pre = drug free; measurements before administration of agent.

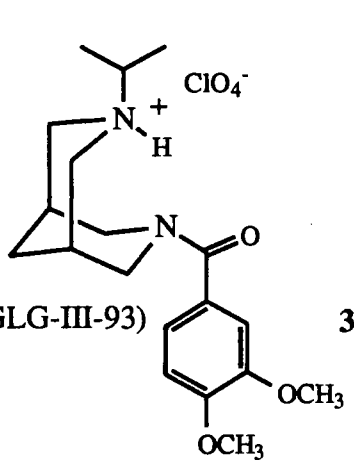
[i]Post = post drug; measurements after the administration of agent.

[j]NE = no effect.

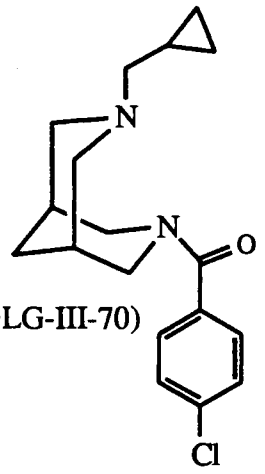
[k]NM = not measured.

observed activity for **38** which was much different than that reported for **29**.[7] In the experiment and after administration of **38**, the MBP increased while the HR was reduced with a prolongation of the VERP, HV, and QT interval (Table XXI). SMVT was found to be noninducible after 3 and 6 mg/kg doses of **38**, and SVT was successfully terminated with 6 mg/kg i.v. These studies suggested that **38** is not only able to prevent but also to terminate PES-induced SMVT.

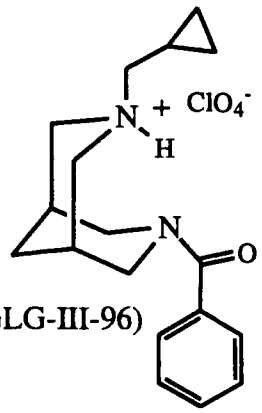
Three other compounds (**14b, 39,** and **42**) were found to have excellent antiarrhythmic activity. All of these compounds possess similar actions with some variation in the degree of effectiveness in terms of the class III parameters measured. One interesting property common to **14b** and **42** is the simultaneous lowering of the HR



14b (GLG-III-93)



39 (GLG-III-70)



42 (GLG-III-96)

and the MBP which suggests that these agents may possess Ca^{+2} channel blocking action (class IV AAA).[7] The data for all these agents (**14b, 39,** and **42**) are also illustrated in Table XXI.

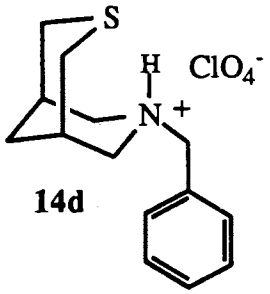
The other eight agents tested showed good class Ib antiarrhythmic activity while their effects on the class III parameters were modest to weak (Table XXII). After the administation (3 mg/kg, i.v.) of **37**, a marked drop in the MBP and the HR was observed. This agent had no effect on any of the class III parameters measured. Interestingly,

TABLE XXII

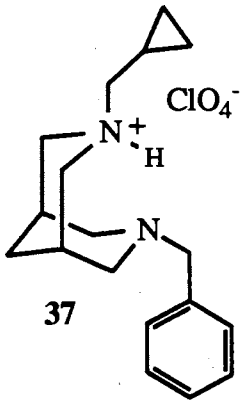
ANTIARRHYTHMIC PROPERTIES[a] OF 3,7-DIHETERABICYCLO[3.3.1]NONANES

Cpd	HR[b]	MBP[c]	QT interval[d]	AH interval[e]	HV interval[f]	VERP[g]	NSVT[h]
14d (BRB-I-28)	NE[i]	INC[j]	NE	NE	INC	INC	3 mg/kg
37 (GLG-IV-17)	DEC[k]	DEC	NM[l]	NM	NM	NM	NM
41 (GLG-IV-74)	NE	DEC	NE	NE	NE	NE	3mg/kg
43 (GLG-III-86)	NE	NE	NE	NE	NE	NE	NE
54a (GLG-V-22)	DEC	DEC	INC	INC	NM	INC	6 mg/kg
54b (GLG-V-18)	DEC	DEC	INC	INC	NM	INC	6 mg/kg
54c (GLG-V-26)	NE	NE	NE	NE	NE	NE	3 mg/kg
56 (GLG-IV-78)	NE	INC	NE	NE	INC	NE	3 mg/kg

[a]Antiarrhythmic properties were compared to lidocaine (3 and 6 mg/kg i.v.) in that lidocaine only reduced the rate of the VT and possessed no other class action.
[b]HR = Heart rate (beats/min).
[c]MBP = Mean blood pressure (mm Hg).
[d]QT interval = Time (msec) elapsed for a cell to undergo depolarization and repolarization.
[e]AH interval = (msec) measures conduction time.
[f]HV interval = (msec) measures sodium channel action.
[g]VERP = (msec) elapsed time to complete the QRS complex of the ECG.
[h]NSVT = NonSustained Ventricular Tachycardia; SVT not inducible at indicated dosage.
[i]NE = no effect.
[j]INC = increased in comparison to drug free state.
[k]DEC = decreased in comparison to drug free state.
[l]NM = not measured.



14d



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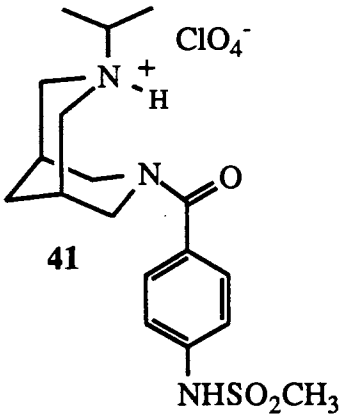

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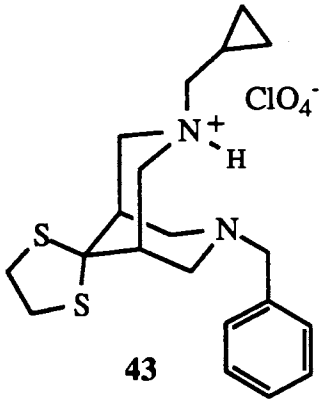
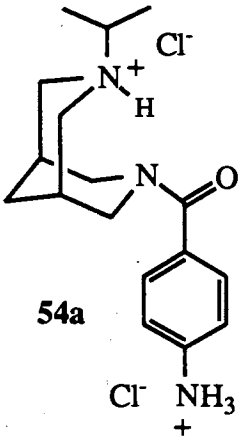
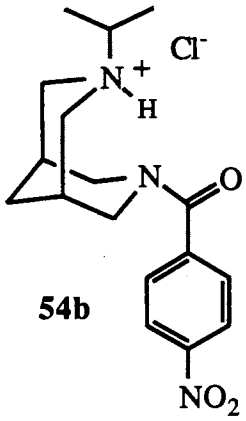


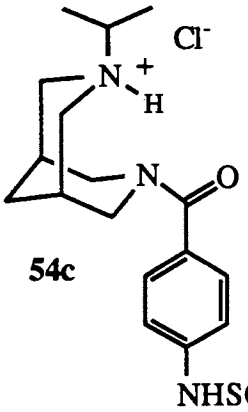
43



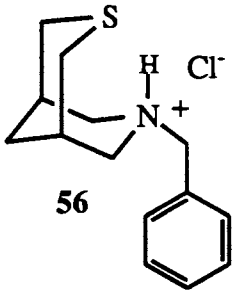
54a



54b



54c



56

compounds **54a** and **54b** all possessed this similar action (decrease MBP and HR; class IV action) but with varying effects on the class III action parameters (Table XXII).

Agents **54a** and **54b** abolished SVT at the 6 mg/kg dose with no pronounced effect seen at 3 mg/kg. Compound **54b** decreased the MBP (95 mm Hg to 70 mm Hg) with fast recovery. The compound induced a lowering of HR (130 beats/min to 110 beats/min) which had a lasting effect of 2 h. It also prolonged HV (35 to 50 msec), VERP (160 to 230 msec), and QT (220 to 260 msec). Similar activities were seen with compound **54a** but the effects were less pronounced.[29]

A comparison of hydroperchlorate **14d** and hydrochloride **56** revealed closely related activities. Salt **14d** induced a significant prolongation of the HV interval (30 to 40 msec) and the VERP (142 to 163 msec) while prolongation by **56** of the HV interval (30 to 35 msec) was less pronounced with no effect on the VERP. Agent **14d** prevented electrically induced sustained monomorphic ventricular tachycardia (SMVT) in 2 of the 6 dogs tested. Salt **14d**, however, markedly slowed the rate of SMVT in the other 4 dogs while **56** had no effect. Both agents **14d** and **56** induced a proarrhythmic effect in the same 2 dogs out of 6 which were tested (the initial VT was abolished, but a new VT was generated). It should be noted that SMVT was not inducible in the drug-free state which indicates that the 2 dogs were not good candidates for the study.

In agents tested (Tables XXi and XXI), one common characteristic feature was that all demonstrated physiological properties coincide with class Ib antiarrhythmic action. Many of these agents were suspected to possess more than one type of class action. Table XXIII is a summary of the electrophysiological data which categorizes the DHBCN examined according to specific class actions. The results indicated in Table XXIII are not absolutely definitive evidence that the agents possess specific class activities. Further electrophysiological studies *in vitro* are required to positively confirm the class actions.

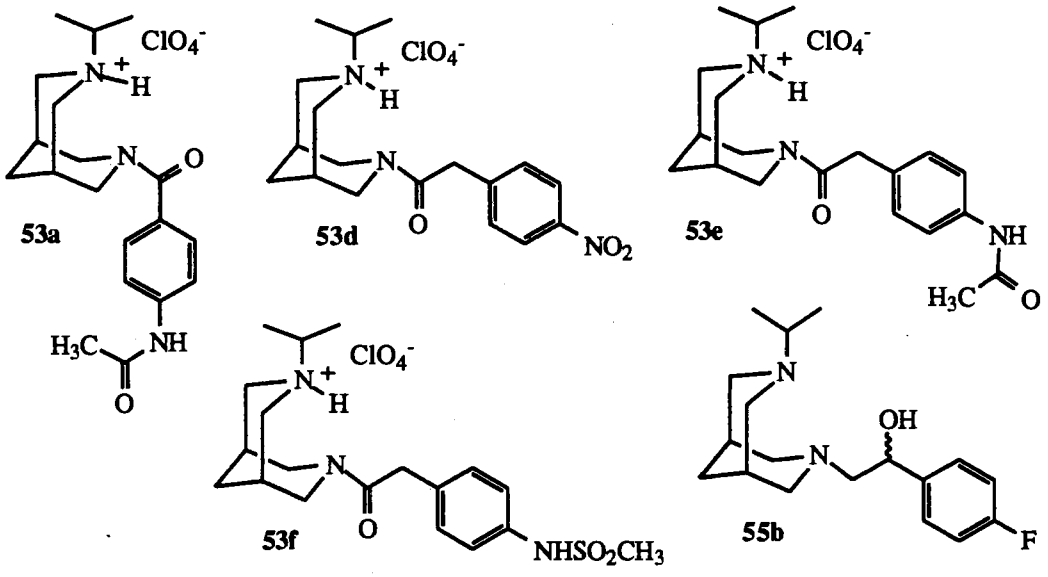
We have recently synthesized several antiarrhythmic agents with the objective to enhance their multiple class actions. The testing of these compounds, namely **53a**, **53d**,

TABLE XXIII

CLASSIFICATION[a] OF
3,7-DIHETERABICYCLO[3.3.1]NONANES

Agent	Class Ib	Class II	Class III	Class IV
14b (GLG-III-93)	Y[b]	N[c]	S[d]	S
14d (BRB-I-28)	Y	N	N	N
37 (GLG-IV-17)	Y	N	N	S
38 (GLG-IV-57)	Y	N	Y	N
39 (GLG-III-70)	Y	N	Y	N
41 (GLG-IV-74)	Y	N	N	N
42 (GLG-III-96)	Y	N	S	S
43 (GLG-III-86)	N	N	N	N
53c (GLG-V-13)	Y	N	Y	S
54a (GLG-V-22)	Y	N	S	S
54b (GLG-V-18)	Y	N	S	S
54c (GLG-V-26)	Y	N	N	N
56 (GLG-IV-78)	Y	N	N	N

[a]Reference 29,83.
[b]Y = agent displayed properties which suggest this type of action.
[c]N = agent gave no indication of possessing such action.
[d]S = agent displayed slight properties of the indicated action.



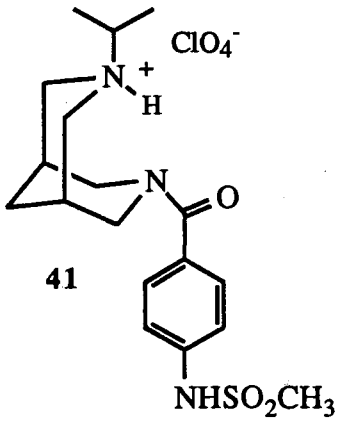
53e, 53f, and **55b**, is currently in progress or will be undertaken. It is predicted that these new agents will exhibit class II, class III, and possibly class IV antiarrhythmic activity along with maintaining the already existing class Ib action.

Structure-Activity Relationships

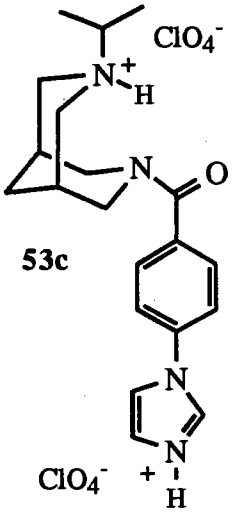
One way to design potential antiarrhythmic agents is by evaluating structure activity relationships (SAR) in families of compounds. After such agents are synthesized and activity data are obtained, modifications of the structures can be meaningful to enhance a biological response and, hopefully, lower the toxicity. With respect to the DHBCN family, SAR have been developed to a fair degree from an accumulation of antiarrhythmic data from infarctions induced in dog models. It has been our intent to examine the SAR data discovered in the aforementioned work and draw some conclusions as to which functional groups are important for useful antiarrhythmic activity, a minimum of proarrhythmic effects, and multiple class action.

Work by Morgan and co-workers[49] implied that the imidazole group might be a

suitable replacement for the sulfonamide moiety to induce class III activity. We prepared compounds **41** and **53c** which differ in structure only with the imidazole or the sulfonamide groups in the para postion. The animal screens revealed that **53c** possessed



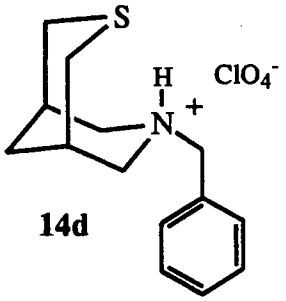
41



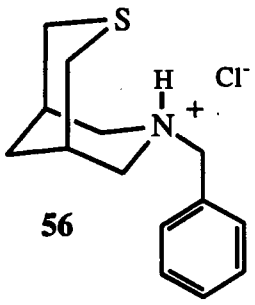
53c

strong class III action as cited previously (Table XXI, page 75). However, agent **41** showed only moderate class Ib action and exhibited no class III antiarrhythmic activity. It appears that the imidazole group possesses better activity in this particular 3,7-diheterabicyclo[3.3.1]nonane derivative. The hydroperchlorates were considered to be the preferred salts in view of the reduced activity of hydrochloride **56** when compared to the corresponding hydroperchlorate **14d**. These findings may only be characteristic of these particular systems and may vary in other DHBCN systems. Additional examples are needed in order to affirm or reject these results.

We developed methodology to obtain hydrochlorides of a few selected 3,7-diheterabicyclo[3.3.1]nonanes in hopes of improving water solubility. After preparing salt **56**, the activity was compared to the known hydroperchlorate **14d** to investigate any differences between the two salts. Salt **14d** was found to have better class Ib AAA than **56**, and **14d** also prolonged the action potential duration and had a longer lasting effect as

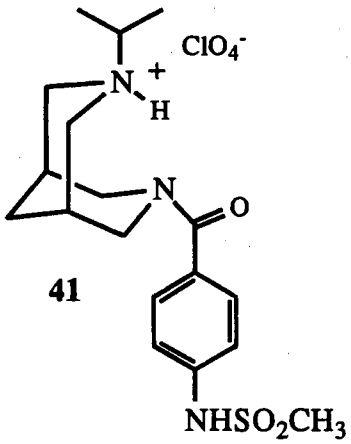


14d

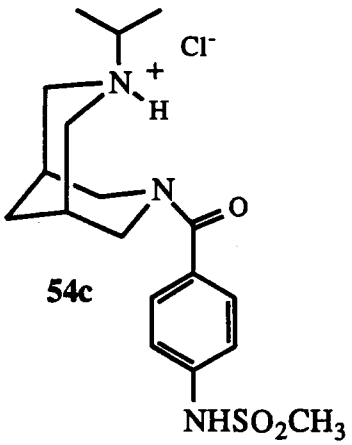


56

compared to **56**. This same kind of evaluation was performed on compounds **41** and **54c** in which slightly different results were obtained. Agent **41** displayed no class III action but had modest class Ib AAA while **54c** did not effect any of the electrophysiological properties (HV, AH, VERP, QRS, and QT) measured. The rationale for the enhanced antiarrhythmic activity of hydroperchlorates versus hydrochlorides remains unknown.

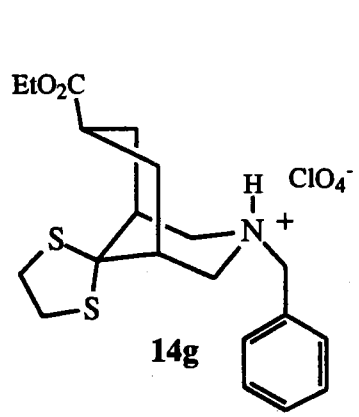


41

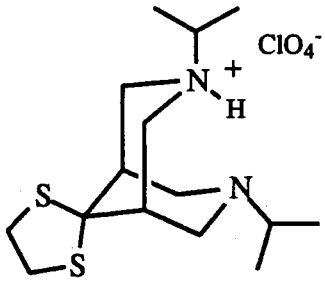


54c

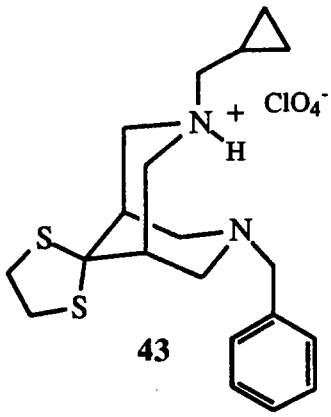
In previously reported work,[8a] thioketal **14g** was found to have good class Ib antiarrhythmic activity in the dog model. On the supposition that **38** and **43** would exhibit similar action, syntheses were initiated and completed. All three agents possess a variety of functional groups, and we had hoped to establish some SAR involving the substituents. The activity of hydroperchlorate **38** was outstanding in that it displayed



14g



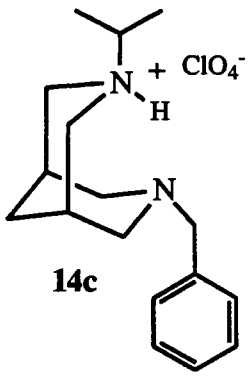
38



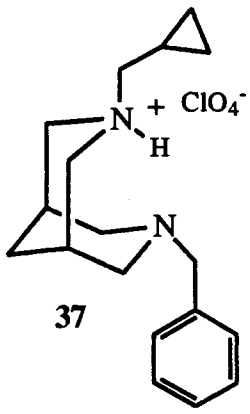
43

both class Ib and class III AAA in dog models. On the other hand, compound **43** possessed no AAA but instead caused acute heart failure in the dog model after administration of 3 mg/kg. From these results, several conclusions can be drawn. Obviously, the different functional groups in **14g** and **43** influence activity. Ester **14g** is a known BC form,[6b] and thus its good activity was unexpected. Apparently the spiro-ring unit fused at C(9) is not detrimental to activity, however, at least in **14g** and **38**. Of course, we can not eliminate the possibility that the particular dog model used with **43** may have been exceptionally vulnerable to sudden death for unidentified reasons. It is always necessary to use several dog models to substantiate activity by an agent.

To evaluate SARs involving the isopropyl group and the cyclopropylmethyl group, a series of DHBCNs containing the cyclopropylmethyl moiety were prepared.[8a] Salts **14c** and **37** were tested and found to have class Ib action, but agent **37** also showed a dramatic



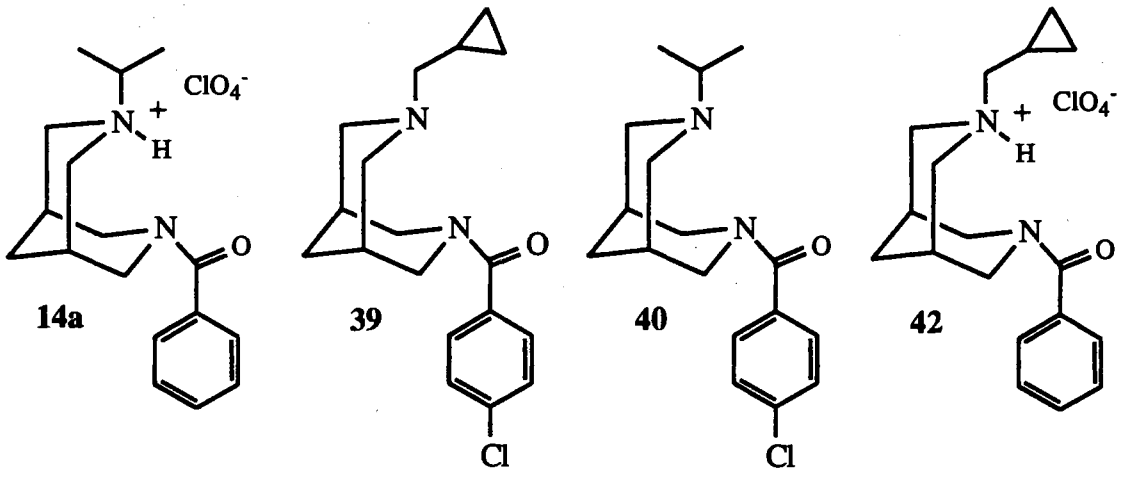
14c



37

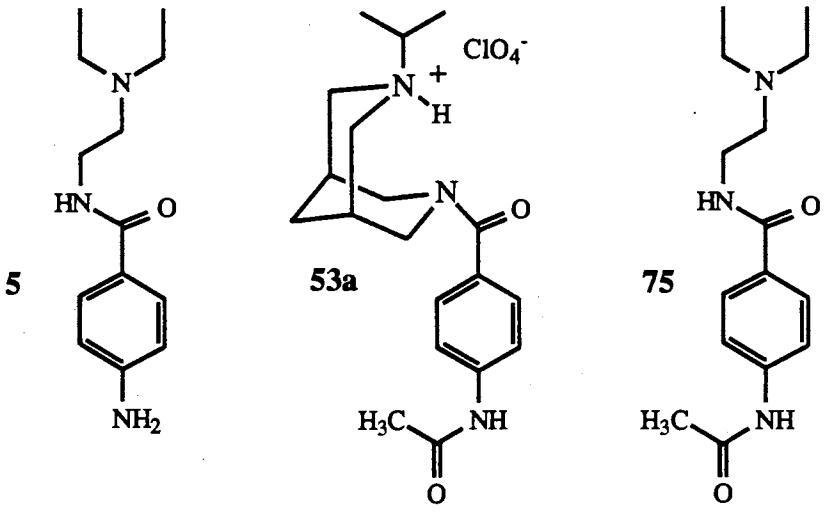
lowering of the heart rate and the blood pressure. These findings suggest that **37** may have some Ca^{+2} channel blocking action. Compounds which possess the ability to block Ca^{+2} channels are sometimes categorized as class IV antiarrhythmic agents.[11]

Amides **39** and **42** also contain a cyclopropyl function. The activities of **39** and **42** were compared to the antiarrhythmic properties of amides **14a** and **40** which possess



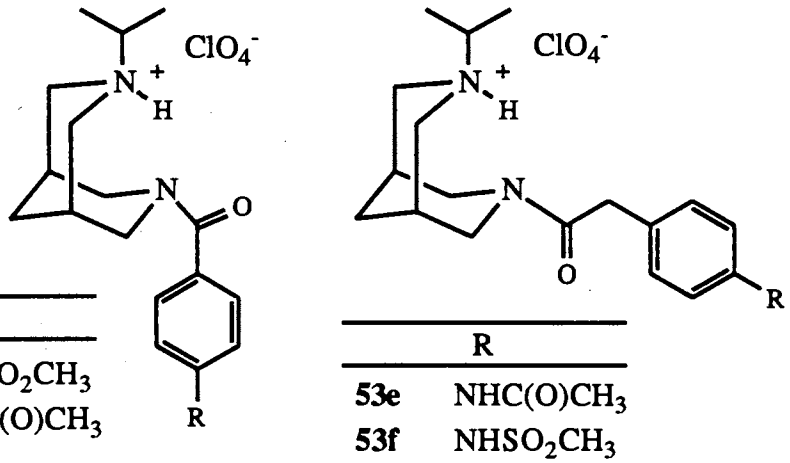
isopropyl groups instead of cyclopropylmethyl moieties All four agents exhibited good class Ib activity, but compounds **39** and **42** were also found to have class III action. Compounds **14a** and **40** were only tested for their class Ib activity, and thus a completely fair comparison of all four agents is not possible at this time. It appears that changing the isopropyl group to the cyclopropylmethyl group does not effect the class Ib action. However, the cyclopropyl group may induce the observed class III action in compound **39**. Agents **14a** and **40** should therefore be tested for class III activity. This would give an indication of which functional group induced the best specific class of antiarrhythmic action.

Currently, several compounds are undergoing electrophysiological testing in which many structural modifications are employed. *N*-Acetylprocainamide (**75**) has been found to be an active metabolite of procainamide (**5**) and which possesses class III AAA.[11]



Conceivably, the incorporation of an *N*-acetyl group could generate class III action in the DHBCN family. Compound **53a** was prepared with this specific purpose in mind. The results from the testing are pending.

Another potential variable to enhance the antiarrhythmic activity of the DHBCN agents could be the distance between the carbonyl group of the amide and the aromatic ring as observed in **53e** and **53f**. The effect of the extra CH_2 group in **53e** and **53f** on antiarrhythmic activity will be compared with that of compounds **41** and **53a**. Several have speculated that a two-carbon bridge between the nitrogen atom and the aromatic

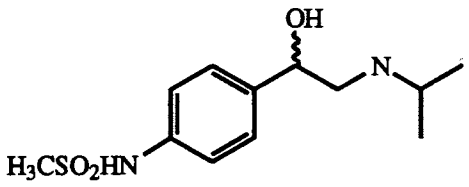


	R
41	$NHSO_2CH_3$
53a	$NHC(O)CH_3$

	R
53e	$NHC(O)CH_3$
53f	$NHSO_2CH_3$

ring may enhance class II antiarrhythmic activity.[11,72,73]

As mentioned earlier, sotalol (**19**) is an antiarrhythmic agent which has multiple class action (class II/III).[20] Structure activity relationships already developed in this series of compounds led to the conclusion that an ethanolamine moiety might be responsible for the observed class II action.[20,67,85] Recall that class II antiarrhythmic activity refers to the slowing of conduction and increasing the effective refractory period.[11] Alcohol **55b** with the ethanolamine function might well possess class II action along with the expected class Ib AAA. Screening for such activity is in progress.



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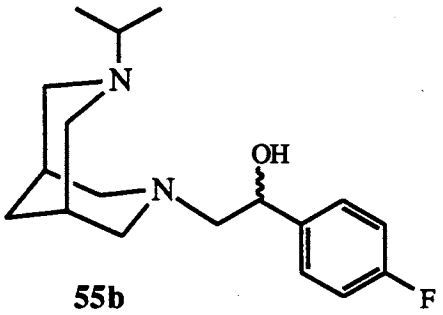


55b

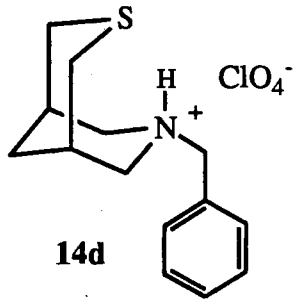
From all of the preceding structure-activity relationships observed, it can be concluded that class Ib activity is inherent in the basic 3,7-diheterabicyclo[3.3.1]nonane system. Structural modifications at the 3- and 7-positions can enhance class Ib action and can add class III activity. Proper alterations in the functional groups attached to nitrogen can produce a multiple class antiarrhythmic activity in a single agent. This muliplicity of action may well be the method of choice in the future treatment of life-threatening arrhythmias which often lead to the "sudden death syndrome".[21,51] Further SAR studies in this family of compounds will be helpful in future work for developing more potent and less toxic anitarrhythmic agents with multi-class antiarrhythmic activity.

Suggestions for Future Work

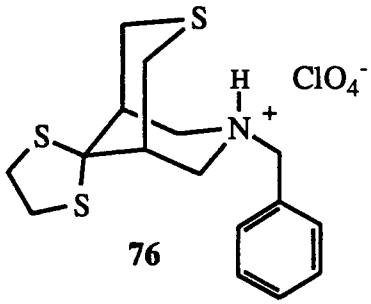
The need for more potent, selective, and less toxic antiarrhythmic agents is significant in spite of the CAST study[63,64] which has reduced public confidence in the

use of antiarrhythmnic agents in general. The synthesis of such compounds can be guided by structure-activity relationships which have been developed to date in a series of DHBCN agents. The low toxicity of some DHBCN in rats has been very encouraging.[29]

Several thioketals in the family of DHBCN have been prepared as previously mentioned. Hydroperchlorate **14d** is known to have good antiarrhythmic activity.[8a] It would be worthwhile to evaluate the effect of masking the 9-position with the thioketal group such as in **76** to determine the influence on the activity. The same concept could

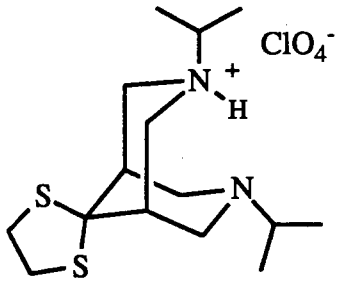


14d

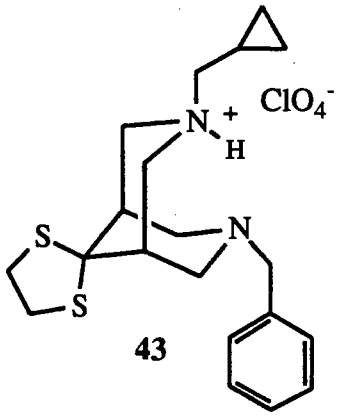


76

be applied to thioketal **77** for comparison of relative activities with those of previously



38



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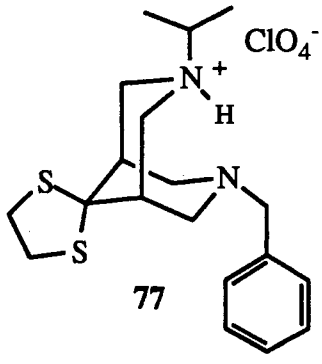
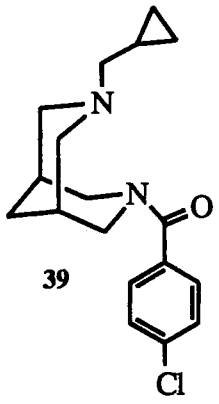
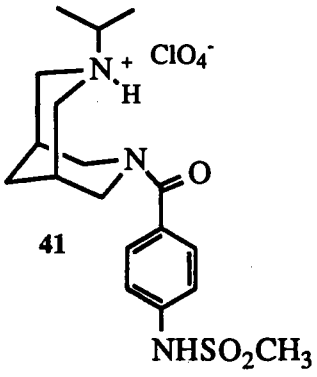


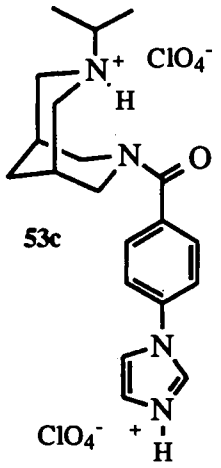
77

prepared thioketals **38** and **43**.

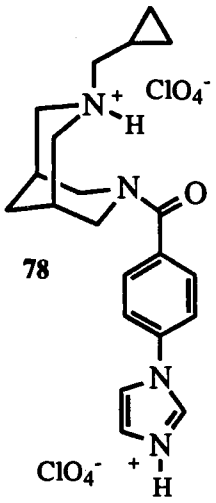
As cited earlier, disalt **53c** exhibited multiple class (Ib and III) antiarrhythmic activity. Agent **39** is believed to possess some class III action along with very good class

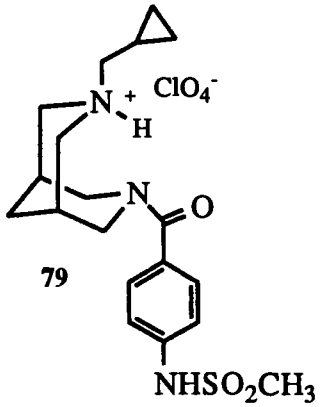






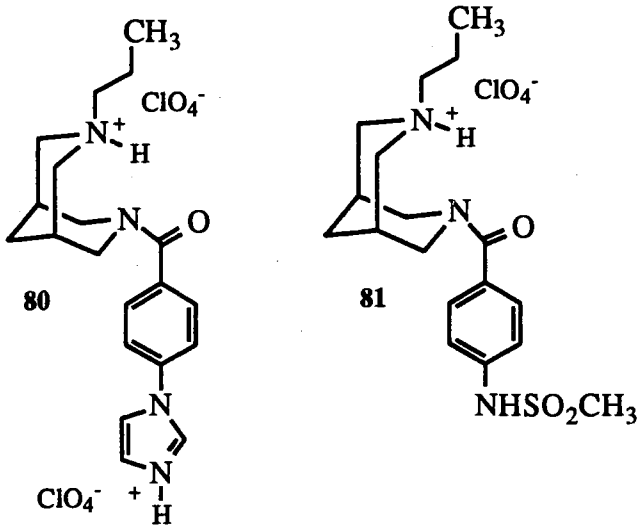
Ib antiarrhythmic activity. The synthesis of amides **78** and **79** would provide agents with the cyclopropylmethyl moiety (present in active **39**) and the imidazole or sulfonamide



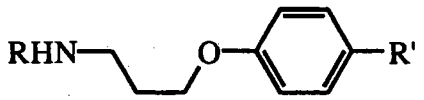


function (present in agents **53c** and **41**, respectively). These structural modifications may very well enhance class III action associated with these individual functional groups and possibly result in greater drug selectivity of action with respect to tissue from which arrhythmias are generated. Likewise, amides **80** and **81** which also incorporate the imidazole and sulfonamide groups are reasonable candidates to possess good

antiarrhythmic activity but their useful properties could also be due to the propyl group which is isomeric with the isopropyl group in **41** and **53c**.



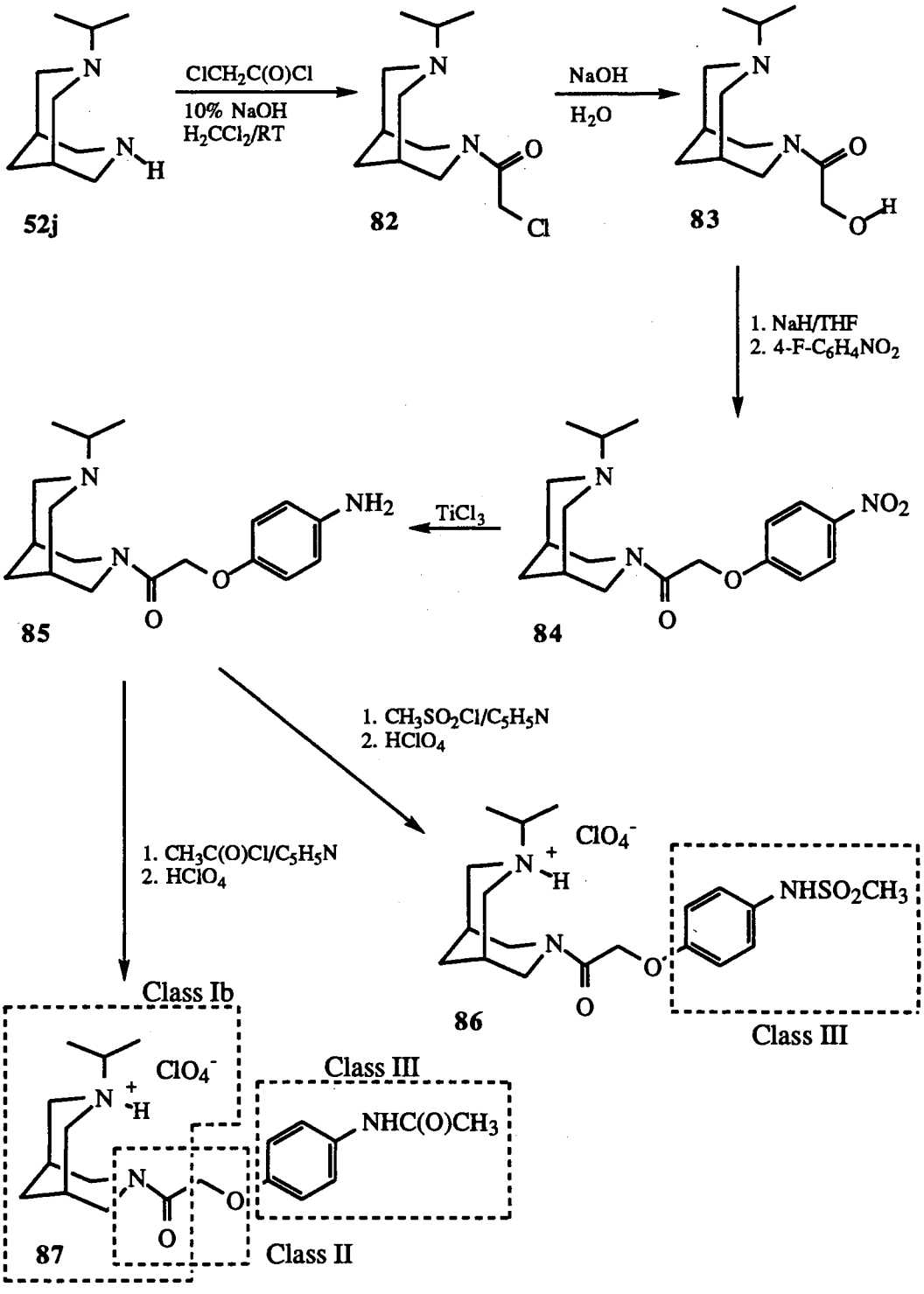
Recently, Morgan and co-workers[44] described the synthesis of (aryloxy)propanolamine derivatives which displayed class II/III AAA. Structure activity relationships suggest that the aryloxy group may be responsible for the observed class II action.



(Aryloxy)propanolamine function

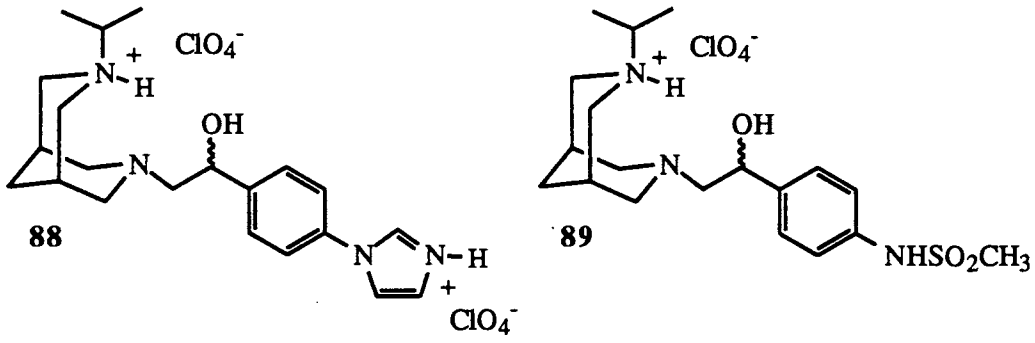
Synthesis of related derivatives could start with the secondary amine **52j** (Scheme XII). Modified Schotten-Baumann conditions using 2-chloroacetyl chloride would give amide **82**. Displacement of the chloride via an SN_2-type reaction using hydroxide ion should yield the corresponding α-hydroxy ketone **83**. Salt formation from **83** and treatment thereof with 4-fluoronitrobenzene should provide **84**. Utilizing procedures similar to those described to obtain **41** and **53a** will generate **85-87** from **84**. It is postulated that agents **86** and **87** (Scheme XII) could possess useful multiple class (Ib/II/III)

SCHEME XII


ClCH2C(O)Cl
10% NaOH
H2CCl2/RT
NaOH
H2O
52j
82
83
1. NaH/THF
2. 4-F-C6H4NO2
TiCl3
NH2
NO2
85
84
1. CH3SO2Cl/C5H5N
2. HClO4
1. CH3C(O)Cl/C5H5N
2. HClO4
ClO4-
NHSO2CH3
86
Class III
Class Ib
Class III
NHC(O)CH3
87
Class II

antiarrhythmic activity on the basis that the 3,7-diheterabicyclo[3.3.1]nonane system alone possesses class Ib action.[6,8,24] Class II activity may be achieved by the (aryloxy)ethanolamine function in view of the class II activity reported[12,44] to be associated with the (aryloxy)propanolamine group. The ethanolamine moiety is believed to be responsible for the class II AAA observed in several different agents.[11,20,67] Imidazole and sulfonamide functionalities have been implicated in the enhancement of class III antiarrhythmic activity.[22,32,45,49,55]

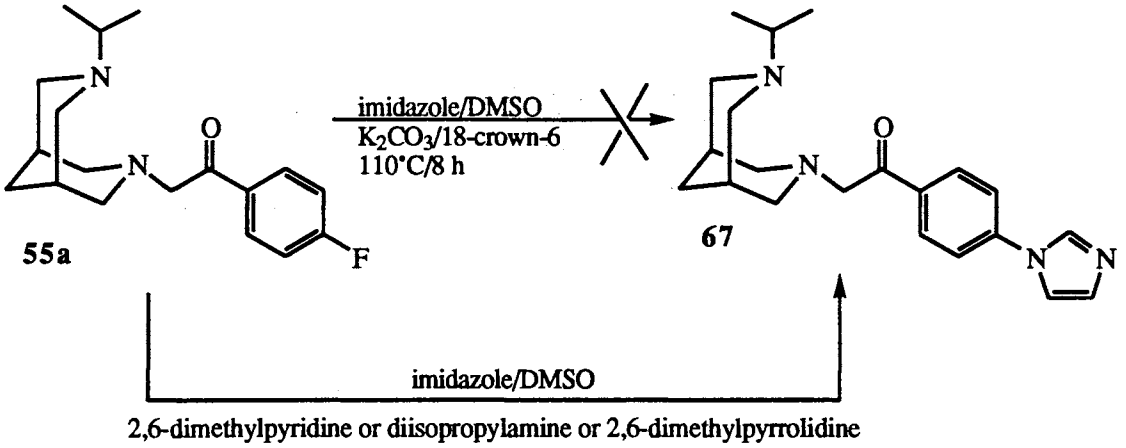
Developing agents which possess multiple class action has become the major area of interest in the preparation of potential antiarrhythmic agents. Synthesis of salts **88** and **89** could possibly possess class Ib (3,7-diheterabicyclop[3.3.1]nonane ring), class II



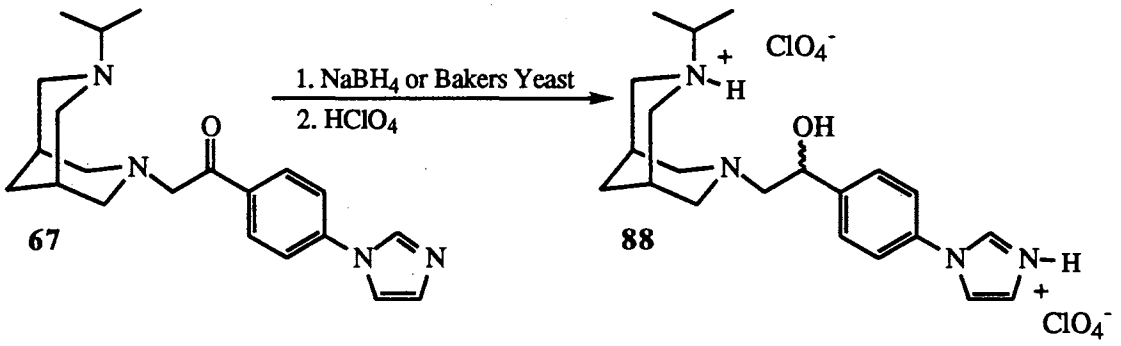
(ethanolamine moiety), and class III (imidazole or sulfonamide groups) activity. Attempts to obtain **88** and **89** have been described (pages 55-57) without success to date.

A key intermediate in the synthesis of **88** is ketone **55a** which has been prepared. It was discovered that the displacement of the fluorine group in ketone **55a** was difficult. Previous attempts to synthesis **67** led to the isolation of starting material **55a**. Preferential removal of the acidic proton in imidazole without generation of the anion on the carbon next to the C=O group may be achievable with exceptionally large and hindered bases such as 2,6-dimethylpyridine, diisopropylamine, 2,6-dimethylpyrrolidine and

diisobutylamine. These reagents have yet to be appraised in this proposed reaction.

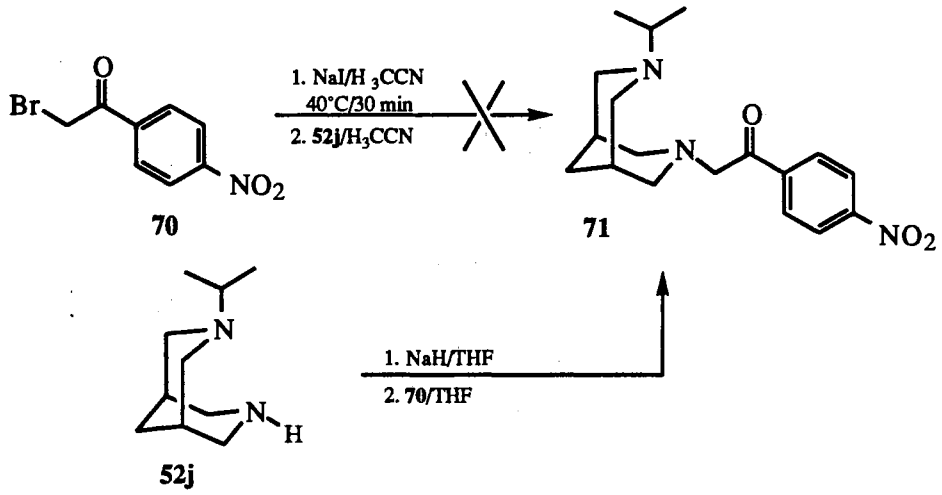


If ketone **67** could be isolated, reduction to **88** should not be difficult since ketone **55a** was smoothly reduced to the corresponding alcohol **55b** with $LiAlH_4$. Such a reduction of ketone **67** to the intermediate alcohol should probably be carried out with $NaBH_4$ since $LiAlH_4$ can reduce C=N linkages (such as present in imidazole) to CH-NH.[47] An approach to a possible chiral *precursor* of **88** from **67** may be realized using Baker's yeast.[69] Selective production of one enantiomeric alcohol over the other is



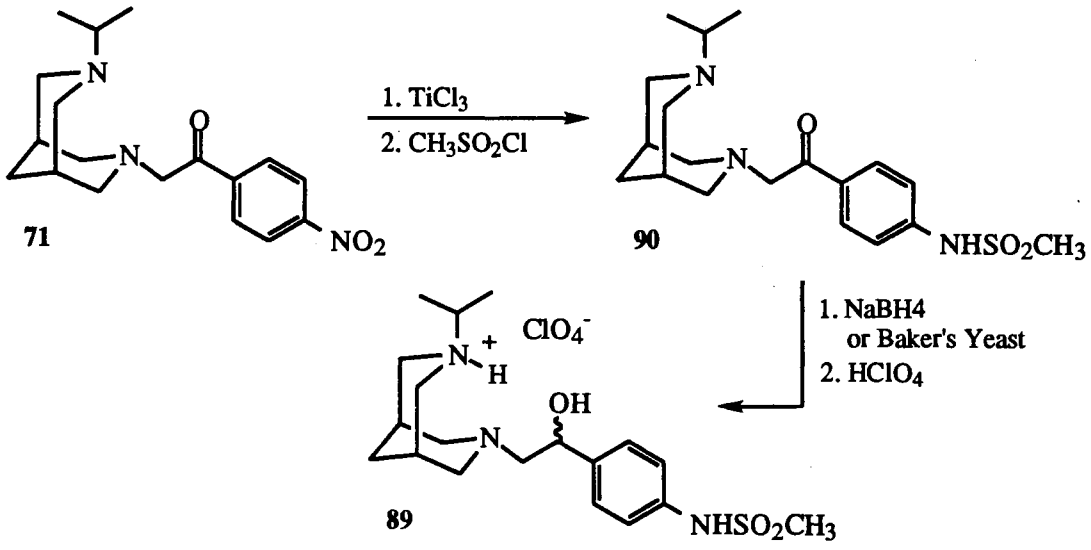
theoretically feasible. Salt **88** would be obtainable directly from the chiral precursor in the usual manner as illustrated. Racemic sotalol (**19**) is prescribed for the treatment of lethal arrhythmias but *d*-sotalol is the active enantiomer.[11,55]

The synthesis of the agent **89** presents a challenge. Attempts to prepare precursor **71** using **52j**, NaI, and α-bromoketone **70** resulted in the recovery of amine **52j**, as previously mentioned. Ketone **71** could possibly be obtain by generating the sodium salt



of **52j** with NaH followed by addition of α-bromoketone **70**. Upon isolation of ketone **71**, reduction of the nitro group (Scheme XIII) to the amine should follow using $TiCl_3$.[77] Formation of the sulfonamide derivative **90** should proceed via conditions already established.[48] Reduction of ketone **90** with mild reagents such as $NaBH_4$ or Baker's yeast could lead to the corresponding racemic or enantiomeric alcohol, respectively.

SCHEME XIII



It is quite possible that any attempt to reduce **90** using $LiAlH_4$ could result in cleavage of the sulfonamide group.[47] Salt **89** should be isolable using standard conditions. Both **88** and **89** are excellent candidates to possess multi-class antiarrhythmic activity.

The projected antiarrhythmic agents above with the indicated modifications may prove to have novel activity. Very recent developments of new antiarrhythmic agents have focused attention on preparing compounds which possess multiple class action. Several compounds from our group were found to have multiple class action with the best agent being **53c**. The suggested new agents **78, 80,** and **86-90** in the DHBCN family may display even greater multiple class and tissue specific antiarrhythmic action as well as useful properties for facile formulation and drug distribution in view of the increased hydrophilic nature of the structures.

CHAPTER III

EXPERIMENTAL SECTION

General Information: Melting points were obtained on a Thomas-Hoover melting point apparatus, an Electrothermal IA9100 digital melting point apparatus, and were uncorrected. IR spectra were recorded on a Perkin-Elmer 681 as KBr pellets or as films. All NMR spectra were taken on an Varian XL-300 BB spectrophotometer with ^{1}H and ^{13}C being observed at 299.94 and 75.43 MHz, respectively. All 2-D and ^{15}N experiments were performed on an XL-400 NMR unit with ^{1}H, ^{13}C, and ^{15}N being observed at 399.99, 100.6, and 41.2 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR spectra were reported in δ or ppm downfield from TMS [$(CH_3)_4Si$)], while ^{15}N NMR signals were reported in ppm downfield from NH_3 (*liquid*, 0 ppm) using 8 M $^{15}NH_4NO_3$ (19.73 ppm) as an external reference. Data have been reported as follows: chemical shifts (in δ values or ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, bs = broad singlet, bd = broad doublet), coupling constants (in Hz), and assignments. Mass spectral data were recorded on a VG analytical instrument model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN 37921.

Syntheses were performed under an atmosphere of N_2 with *magnetic stirring* unless otherwise specified. The following reagents were obtained commercially and used without further purification: (aminomethyl)cyclopropane (Aldrich), 2-chloro-4'-fluoro-acetophenone (Aldrich), glacial acetic acid (Dupont), hydrazine (95%, Fisher), hydrochloric acid (Mallinckrodt), imidazole (Aldrich), isopropylamine (Aldrich), $LiAlH_4$ (95%, Aldrich), 4-nitrobenzoyl chloride (Aldrich), 4-nitrophenylacetic acid (Aldrich),

methanesulfonyl chloride (Aldrich), Pd/C (10%, Alfa), paraformaldehyde (Fisher) perchloric acid (60%, Baker), potassium carbonate (EM Science), potassium hydroxide (85%, Baker), PTSA (Fisher), sodium azide (Fisher), sodium chloride (Mallinckrodt), sodium hydroxide (97%, Fisher), sodium iodide (Fisher), titanium trichloride (12% $TiCl_3$ in HCl, Aldrich), and 18-crown-6 (Aldrich). The following compounds required distillation prior to use: benzoyl chloride (bp 46°C/1.0 mm Hg, Eastman), benzylamine (bp 57-59°C/4.25 mm Hg, Lancaster), 4-chlorobenzoyl chloride (bp 40°C/10 mm Hg, Aldrich), 1,2-ethanedithiol (bp 144-146°C, Aldrich), 4-fluorobenzoyl chloride (82°C/20 mm Hg, Aldrich), *N*-benzyl-4-piperidone (bp 134°C/7.0 mm Hg, Aldrich), and *N*-isopropyl-4-piperidinone (bp 100-101°C/27 mm Hg mm Hg, Lancaster), and pyridine (114°C, Fisher). Ammonium formate (Baker) was recrystallized from methanol (mp 118-120°C). Reagent grade solvents were used without further purification and chromatographic separations were done on silica gel ("Davisil 62", 60-200 mesh, Davison Chemical) and alumina (neutral, 70-230 mesh, Merck). **Caution:** *Although no difficulties were experienced in handling hydroperchlorates, extreme care should be used at all times and all the work should be carried out in the hood behind a protective shield since salts of this nature are potentially explosive.*

7-Benzyl-3-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (37). A 250-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C, ice bath) solution of amine **47b** (4.41 g, 16.31 mmol) in dry ether (150 mL) was added $HClO_4$ (60%, 3.41 g , 20.39 mmol) dropwise over a period of 15 min. The mixture was allowed to stir an additional 15 min at 0-5°C. A white precipitate formed and was filtered and washed with cold ether (30 mL). The solid was recrystallized (H_3COH, 30 mL), and white needles were collected and washed with cold H_3COH (25 mL) and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 4.3 g (71.1%)

of salt **37**; mp 190-191°C. IR (KBr) 3060, 3005 (ArH), 2910, 2820 (C-H), 1100 (Cl-O), 735, 710 (C-H out of plane, mono) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.46 [m, 2 H, $(CH_2)_{ax}$, cyclopropyl ring], 0.62 [m, 2 H, $(CH_2)_{eq}$, cyclopropyl ring], 1.07 [m, 1 H, (*CH*), cyclopropyl ring], 1.64 [d, J = 11.4 Hz, 1 H, $H(9)_{ax}$], 1.77 [d, J = 11.4 Hz, 1 H, $H(9)_{eq}$], 2.42 [d, J = 11.1 Hz, 2 H, $H(6,8)_{ax}$], 2.85 (d, J = 7.2 Hz, 2 H, CH_2-cyclopropyl), 3.09 [m, 4 H, $H(2,4)_{ax}$, $H(6,8)_{eq}$], 3.54 [bs, 4 H, CH_2-Ar, $H(2,4)_{eq}$], 7.31-7.43 (m, 5 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 3.87 (CH_2, cyclopropyl ring), 6.07 (*C*H, cyclopropyl ring), 27.46 [C(6)], 29.58 [C(1,5)], 57.01, 56.84 [C(2,4,6,8)], 60.56 (CH_2-Ar), 61.49 (NCH_2-cyclopropyl), 127.57, 128.39, 129.32, 136.49 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 49.22 [N(7)], 55.18 [N(3)]. Mass spectral (EI) data calcd for $C_{18}H_{27}ClN_2O_4$ *m/z* (M^+): 270.2096 (-$HClO_4$). Found: 270.2093. Anal. Calcd for $C_{18}H_{27}ClN_2O_4$: C, 58.29; H, 7.34. Found: C, 58.39; H, 7.30.

3,7-Diisopropyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (38). Into a 250-mL, Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was placed thioketal **49a** (8.06 g, 26.82 mmol) in dry ether (100 mL), and the solution was cooled to 0-5°C in an ice bath. To the stirred solution was added $HClO_4$ (60%, 5.61 g, 33.52 mmol) dropwise over a period of 15 min . After stirring an additional 15 min at 5°C, the solution deposited a white precipitate which was filtered (suction) and washed with cold ether (25 mL). Recrystallization (hot H_3COH, 50 mL) afforded, after drying (Abderhalden, 80°C/0.2 mm Hg, P_2O_5, 12 h), hydroperchlorate **38** as white needles (3.15 g, 29.3%); mp 222.0-223.0°C. IR (KBr) 2980, 2920, 2820 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.18 (d, J = 6.4 Hz, 12 H, CH_3 isopropyl), 2.31 [bs, 2 H, H(1,5)], 3.32-3.57 [m, 15 H, N-*H*, $H(2,4,6,8)_{ax-eq}$, C-*H* isopropyl, S-CH_2]; ^{13}C NMR ($DCCl_3$) ppm 16.78 (CH_3 isopropyl), 39.29 [C(1,5)], 41.23 (S-CH_2), 52.29 [C(2,4,6,8)],

54.64 (*C*-H isopropyl), 70.22 [C(9)]; Anal. Calcd for $C_{15}H_{29}ClN_2S_2O_4$: C, 44.93; H, 6.99; S, 15.99. Found: C, 45.10; H, 7.33; N, 6.91; S, 15.80.

3-(4-Chlorobenzoyl)-7-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonane (39)

A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with N_2 inlet, a 25-mL addition funnel, and two glass stoppers. To a mixture of amine **47c** (4.03 g, 22.35 mmol) in H_2CCl_2 (25 mL) and 10% NaOH (22.41 g, 55.88 mmol) was added dropwise a solution of 4-chlorobenzoyl chloride (4.30 g, 24.59 mmol) in H_2CCl_2 (15 mL) over a period of 30 min. Stirring (magnetic) of the mixture was continued for an additional 3 h under N_2. To the heterogenous mixture was added H_2O (100 mL) and two layers separarated. Further extracts (H_2CCl_2, 3 x 50 mL) of the aqueous layer were combined, dried (Na_2SO_4, 1 h), filtered and concentrated (rotary evaporator) to give a viscous yellow oil. Flash chromatography of the oil was performed on neutral alumina (50 g, 60-mL fritted funnel, aspirator) using hexanes:ethyl acetate (60:40) as the eluent. The filtrate was concentrated (rotary evaporator) and then placed on vacuum pump overnight (RT/0.2 mm Hg) to give 4.18 g (83.1 %) of an off-white solid **39**; mp 67-68°C. IR (KBr) 3090, 3005 (ArH), 2920, 2880, 2770 (C-H), 1635 (NC=O), 760 (C-H out of plane, para) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.12 [m, 2 H, (CH_2)$_{ax}$, cyclopropyl ring], 0.54 [m, 2 H, (CH_2)$_{eq}$, cyclopropyl ring], 0.91 [m, 1 H, (*CH*), cyclopropyl ring], 1.73 [m, 3 H, H(5), H(9)], 2.02 [m, 2 H, H(1), CH_2-cyclopropyl], 2.24 [m, 3 H, H(4)$_{ax}$, H(6)$_{ax}$, CH_2-cyclopropyl], 2.96 [d, J = 10.5 Hz, 1 H, H(6)$_{eq}$], 3.03 [d, J = 13.2 Hz, 1 H, H(2)$_{ax}$], 3.28 [m, 2 H, H(8)$_{ax}$, H(4)$_{eq}$], 3.75 [d, J = 13.2 Hz, 1 H, H(8)$_{eq}$], 4.83 [d, J = 13.2 Hz, 1 H, H(2)$_{eq}$], 7.39 (s, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.21, 4.43 (CH_2 cyclopropyl), 8.29 (*C*H cyclopropyl), 29.01 [C(1)], 29.41 [C(5)], 32.10 [C(9)], 46.59 [C(2)], 52.16, 58.10, 58.38 [C(4,6,8)], 64.25 (N*C*H$_2$-cyclopropyl), 128.15, 128.28, 134.40, 135.90 (Ar-*C*), 169.06 (N*C*=O); ^{15}N NMR ($DCCl_3$) ppm 40.55 [N(7)], 119.74

[N(3)]; Mass spectral (EI) data calcd for $C_{18}H_{23}ClN_2O$ *m/z* (M^+): 318.1499. Found: 318.1498. Anal. Calcd for $C_{18}H_{23}ClN_2O$: C, 67.81; H, 7.27; N, 8.79. Found: C, 67.53; H, 7.25; N, 8.72.

3-[4-(Methylsulfonyl)amino]benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (41). To a 250-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was added sulfonamide **52c** (3.1 g, 8.48 mmol) dissolved in EtOH (95%, 50 mL), and the resulting solution was chilled (5°C). With stirring, $HClO_4$ (60%, 1.77 g, 10.60 mmol) in EtOH (5 mL) was added dropwise over a period of 15 min, and stirring was continued an additional 10 min at this temperature. The white precipitate was suction filtered and recrystallized from warm H_2O (25 mL) to give 1.97 g (49.9%) of white platelettes of **41**; mp 267-268°C. IR (KBr) 3260, 3120 (N-H), 3010 (Ar-H), 2940, 2880 (C-H), 1630 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (dd, J = 6.1 Hz, 2 H, C*H*$_3$ isopropyl), 1.69-1.87 [dd, 2 H, H(9)], 2.24 [m, 2 H, H(1,5)], 3.06 (s, 3 H, SO_2CH_3), 3.18-3.55 (m, 9 H, ring protons, C-*H* isopropyl), 7.24 (bd, 2 H, Ar-*H*), 7.37 (bd, 2 H, Ar-*H*), 7.93 (bs, 1 H, N-*H*), 10.05 (s, 1 H, CH_3SO_2N-*H*); ^{13}C NMR (DMSO-d_6) ppm 26.48 (*C*H$_3$ isopropyl), 27.59 [C(1,5,9)], 59.53 [bs, *C*-H isopropyl, C(2,4,6,8), *C*H$_3$SO$_2$], 118.12, 128.81, 130.60, 139.53 (Ar-*C*), 172.62 (N*C*=O); Mass spectral (EI) data calcd for $C_{18}H_{28}ClN_3SO_7$ *m/z* (M^+): 365.1773 (-$HClO_4$). Found: 365.1775. Anal. Calcd for $C_{18}H_{28}ClN_3SO_7$: C, 46.40; H, 6.06; N, 9.02; S, 6.88. Found: C, 46.40; H, 6.01; N, 8.94; S, 7.07.

3-Benzoyl-7-cyclopropylmethyl-3,7-diazabicyclo-[3.3.1]nonane Hydroperchlorate (42). A 250-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C, via ice bath) stirred solution of the amide **50** (7.15 g, 25.14 mmol) in dry ether (120 mL) was added dropwise a solution of $HClO_4$ (60%, 5.26 g,

31.43 mmol) over a 10-min period followed by stirring for an additional 10 min. Filtered salt **42** (a white solid) was washed with dry, cold ether (60 mL). The white solid was recrystallized (hot H_3COH, 160 mL) and filtered hot and then allowed to cool to RT. Filtration and drying (Abderhalden, 0.2 mm Hg/80°C, 12 h) afforded 6.30 g (65.1%) of pure salt **42**; mp 236.0-237.0°C. IR (KBr) 3150 (N-H), 3020 (Ar-H), 2840, 2880 (C-H), 1630 (NC=O), 1095 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 0.52 [d, J = 3.1 Hz, 2 H, cyclopropyl $CH_{2\ ax}$], 0.81 [d, J = 2.7 Hz, 2 H, cyclopropyl $CH_{2\ eq}$], 1.19 (m, 1 H, cyclopropyl C-*H*), 1.83 [bd, 1 H, H(1)], 2.24 [bd, 3 H, H(5,9)], 2.98 (d, J = 6.2 Hz, 2 H, CH_2 cyclopropyl), 3.21 (m, 4 H, ring protons), 3.71 (bs, 2 H, ring protons), 4.08 (bs, 2 H, ring protons), 7.41 (m, 5 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 5.27 (cyclopropyl CH_2), 26.45 [C(1,5)], 27.76 [C(9)], 62.56 [C(2,4,6,8), CH_2-cyclopropyl], 126.95, 128.22, 129.33, 136.98 (Ar-*C*), 172.69 (N*C*=O); ^{15}N NMR (DMSO-d_6) ppm 50.05 [N(7)], 108.49 [N(3)]; Mass spectral (EI) data calcd for $C_{18}H_{25}ClN_2O_5$ *m/z* (M^+): 284.1888 (-$HClO_4$). Found: 284.1888. Anal. Calcd for $C_{18}H_{25}ClN_2O_5$: C, 56.18; H, 6.55. Found: C, 55.92; H, 6.57.

7-Benzyl-3-cyclopropylmethyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]-nonane Hydroperchlorate (43). Into a 250-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was placed thioketal **49b** (6.44 g, 17.86 mmol) in dry ether (100 mL), and the solution was cooled to 0-5°C (ice bath). To the stirred mixture was added dropwise perchloric acid (60%, 3.73 g, 22.32 mmol) over a period of 15 min. After stirring an additional 15 min at 5°C, a white precipitate formed and was filtered (suction) and washed with cold ether (25 mL). Recrystallization was effected by dissolving the white solid in hot H_3COH (50 mL) to afford, after drying (Abderhalden, 80°C, 0.2 mm Hg, P_2O_5, 12 h), hydroperchlorate **43** (3.34 g, 40.6%) as white needles; mp 147.5-149.0°C. IR (KBr) 3090, 3010 (ArH), 2940, 2850 (C-H), 1100 (Cl-O), 735, 705

(C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.59 [m, 2 H, (CH_2)$_{ax}$, cyclopropyl ring], 0.68 [m, 2 H, (CH_2)$_{eq}$, cyclopropyl], 0.98 (m, 1 H, C-*H* cyclopropyl ring), 2.26 [bs, 2 H, H(1,5)], 3.01 [m, 4 H, H(2,4)$_{ax}$, CH_2-cyclopropyl], 3.31-3.46 [m, 8 H, H(6,8)$_{ax}$, H(2,4)$_{eq}$, SCH_2], 3.73 (s, 2 H, Ar-CH_2), 3.92 [d, J = 13.1 Hz, 2 H, H(6,8)$_{eq}$], 7.28-7.45 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 4.29 (CH_2, cyclopropyl ring), 6.10 (*C*H, cyclopropyl ring), 39.19, 39.35 (SCH_2), 41.73 [C(1,5)], 56.12 [C(2,4)], 56.92 [C(6,8)], 60.96 (Ar-CH_2), 60.99 (CH_2-cyclopropyl), 69.42 [C(9)], 128.04, 128.57, 129.89, 135.09 (Ar-*C*); Mass spectral (EI) data calcd for $C_{20}H_{29}ClN_2O_4S_2$ *m/z* (M^{+}): 360.1694 (-$HClO_4$): Found: 360.1703. Anal. Calcd. for $C_{20}H_{29}ClN_2O_4S_2$: C, 52.10; H, 6.34; N, 6.08; S, 13.91. Found: C, 51.98; H, 6.30; N, 5.81; S, 14.05.

3-(4-Aminobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (44). To a 500-mL, Erlenmeyer flask equipped with a magnetic stirrer was added amide **52a** (9.17 g, 28.90 mmol) in AcOH/H_2O (1:1, 100 mL). To this solution was added in one portion $TiCl_3$ (12%, 195.0 g, 202.3 mmol), and the mixture was stirred at RT for 7 min. The deep purple solution was basified (pH~12) with 20% NaOH until a dark blue color persisted. Extraction (H_2CCl_2, 4 x 90 mL) was followed by washing with H_2O (2 x 100 mL) and brine (100 mL). After drying (Na_2SO_4, 2 h), the solution was filtered and concentrated (rotary evaporator) to give 7.34 g (86.2%) of an off-white solid **44**; mp 149-150°C. IR (KBr) 3340, 3220 (N-H), 3060, 3020 (Ar-H), 2980, 2920, 2800 (C-H), 1640 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.98 (bs, 6 H, CH_3 isopropyl), 1.67 [m, 3 H, H(5), H(9)], 1.91 [s, 1 H, H(1)], 2.41 (bs, 2 H, ring proton), 2.59 (m, 1 H, C-*H* isopropyl), 2.72 (s, 1 H, ring proton), 3.02 (bs, 2 H, ring protons), 3.31 (d, 1 H, ring proton), 3.83 (bs, 3 H, NH_2, ring proton), 4.70 (bd, 1 H, ring proton), 6.62 (d, 2 H, Ar-*H*), 7.19 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.81, 18.79 (CH_3 isopropyl), 29.15, 29.79 [C(1,5)], 32.25 [C(9)], 46.61 [C(2)], 52.59, 54.22 [C(4,6,8), *C*-H isopropyl], 114.10, 127.21, 128.68,

147.18 (Ar-*C*), 170.47 (N*C*=O); Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.05; H, 8.77; N, 14.62. Found: C, 70.67; H, 8.82; N, 14.28.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (46a). A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 250-mL addition funnel, a condenser with N_2 inlet, and a glass stopper. A mixture of isopropylamine (8.87 g, 150.0 mmol) HCl (37%, 7.39 g, 75.0 mmol), glacial acetic acid (9.01 g, 150.0 mmol) and parformaldehyde (9.46 g, 315.0 mmol) in deoxygenated (dry N_2 was bubbled through the solvent for 2 h) H_3COH (125 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-isopropyl-4-piperidinone (**45a**, 21.18 g, 150.0 mmol), and glacial acetic acid (9.01 g, 150.0 mmol) was added dropwise over a period of 1.5 h, which was followed by a period of boiling for an additional 23 h. After the initial 10 h of heating, more paraformaldehyde (9.46 g, 315.0 mmol) was added in one portion to the mixture after which reflux was continued for an additional 13 h. After cooling to room temperature, concentration (rotary evaporator) of the solution (after 23 h) gave an orange oil which was redissolved in H_2O (150 mL), and extracts (ether, 2 x 100 mL) thereof were discarded. The aqueous layer was chilled (5°C) in an ice bath and made basic (pH~12) with NaOH pellets. Extraction (H_2CCl_2, 3 x 75 mL) gave a solution which was dried (Na_2SO_4, 2 h), filtered, and concentrated (rotary evaporator) to give a viscous, reddish-orange oil. Distillation of the oil under reduced pressure (110-120°C/10^{-5} mm Hg) gave 22.53 g (67.3%) of a light yellow oil **46a**. IR (film) 2975, 2910, 2830 (C-H), 1735 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.02 (d, J = 6.5 Hz, 12 H, C*H*$_3$ isopropyl), 2.58 [m, 2 H, H(1,5)], 2.87 [m, 6 H, H(2,4,6,8)$_{ax}$, C-*H* isopropyl], 3.04 [dd, J = 10.1 Hz, 4 H, H(2,4,6,8)$_{eq}$]; ^{13}C NMR ($DCCl_3$) ppm 17.90, 18.02 (*C*H$_3$, isopropyl), 46.82 [C(1,5)], 53.17 (*C*-H isopropyl), 53.27, 53.36 [C(2,4,6,8)], 215.18 [C(9)]. Anal. Calcd for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.39; H, 10.61; N, 12.21.

7-Benzyl-3-cyclopropylmethyl-3,7-diazabicyclo-[3.3.1]nonan-9-one (46b). A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 250-mL addition funnel, a condenser with N_2 inlet, and a glass stopper. A mixture of (aminomethyl)cyclopropane (4.44 g, 62.4 mmol), HCl (37%, 3.07 g, 31.2 mmol), glacial acetic acid (3.75 g, 62.4 mmol) and parformaldehyde (3.94 g, 131.04 mmol) in deoxygenated (N_2 bubbled in for 2 h) CH_3OH (125 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**45b**, 11.8 g, 62.4 mmol) and glacial acetic acid (3.75 g, 62.4 mmol) was added dropwise over a period of 1.5 h. After 10 h at reflux, the mixture was treated with additional paraformaldehyde (3.94 g, 131.04 mmol) in one portion. Heating at reflux was continued for another 19 h. Upon cooling to RT, concentration (rotary evaporator) of the solution gave a orange oil which was dissolved in H_2O (100 mL). Extracts (ether, 2 x 75 mL) of the aqueous solution were discarded. The aqueous layer was chilled (5°C) in an ice bath and made basic (pH~12) with NaOH pellets. Extraction (H_2CCl_2, 3 x 75 mL) gave a solution which was dried (Na_2SO_4, 2 h), filtered, and concentrated (rotary evaporator) to a viscous, reddish-orange oil. Distillation of the oil under reduced pressure (175-190°C/10^{-5} mm Hg) gave 13.54 g (76.3%) of **46b** as an light yellow oil which solidified upon standing at -10°C; mp 56.0-57.5°C. This solid was recrystallized (hot pentane) to give an analytical sample; mp 58.5-59.5°C. IR (KBr) 3090, 3070, 3030 (Ar-H), 3005 (C-H, cyclopropyl), 2975, 2910, 2830 (C-H), 1740 (C=O), 1600, 1495 (ArC=C), 740, 710 (C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.12 [m, 2 H, (C-*H*)$_{ax}$, cyclopropyl ring], 0.51 [m, 2 H (C-*H*)$_{eq}$, cyclopropyl ring], 0.89 [m, 1 H, (C-*H*), cyclopropyl ring], 2.32 (d, J = 9.8 Hz, 2 H, C*H*$_2$-cyclopropyl), 2.59 [m, 2 H, H(1,5)], 2.81 [dd, J = 10.8 Hz, J = 5.6 Hz, 2 H, H(6,8)$_{ax}$], 2.94 [dd, J = 10.8 Hz, J = 6.8 Hz, 2 H, H(2,4)$_{ax}$], 3.04 [dd, J = 10.8 Hz, J = 3.2 Hz, 2 H, H(6,8)$_{eq}$], 3.12 [dd, J = 10.8 Hz, J = 3.2 Hz, 2 H, H(2,4)$_{eq}$], 3.57 (s, 2 H, C*H*$_2$Ph), 7.38-7.22 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.76 (*C*H$_2$, cyclopropyl ring), 8.53 (*C*H, cyclopropyl ring), 46.76 [C(1,5)], 58.19 [C(2,4)], 58.36 [C(6,8)], 61.11

(CH_2Ph), 61.85 (CH_2-cyclopropyl), 127.08, 128.22, 128.66, 138.54 (Ar-*C*), 214.85 [*C*=O]; ^{15}N NMR ($DCCl_3$) ppm 36.17 [N(7)], 37.74 [N(3)]; Mass spectral (EI) data calcd for $C_{18}H_{24}N_2O$ *m/z* (M^+): 284.1188; Found: 284.1190. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.19; H, 8.46; N, 9.99.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane (47a). A 200-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condensor with N_2 inlet, and two glass stoppers. To a solution of ketone **46a** (5.90 g, 20.3 mmol) in triethylene glycol (60 mL) was added KOH pellets (85%, 13.89 g, 210.9 mmol) and hydrazine (95%, 3.55 g, 105.19 mmol). The stirred mixture was heated at 160-170°C for 4 h under N_2 via the use of boiling tetralin (bp 207°C) in the jacket. Cooling the solution to RT (1 h) was followed by addition of chilled H_2O (100 mL). Extraction (ether, 4 x 50 mL) was followed by washing the combined extracts with 10% NaOH (100 mL), and satd NaCl (100 mL) and then drying (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) of the solution gave a light yellow oil **47a** (4.48 g, 81.1%) which was placed on a vacuum pump overnight (RT/0.2 mm Hg). IR [(film) 2975, 2900, 2820 (C-H) cm^{-1}] analysis of compound showed no carbonyl absorption as present in the starting material **46a**, and thus **47a** was used without further purification to prepare salt **48.**

7-Benzyl-3-cyclopropylmethyl-3,7-diazabicyclo-[3.3.1]nonane (47b). A 200-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condensor with N_2 inlet, and two glass stoppers. To a solution of ketone **46b** (9.53 g, 33.51 mmol) in triethylene glycol (100 mL) was added KOH pellets (85%, 17.7 g, 268.08 mmol) and hydrazine (95%, 4.52 g, 134.04 mmol). The stirred mixture was heated at 160-170°C for 4 h under N_2 via the use of boiling tetralin (bp 207°C) in the

jacket. Cooling the solution to RT (1 h) was followed by addition of chilled H_2O (100 mL). Combined extracts (ether, 4 x 80 mL) of the suspension were first washed with 10% NaOH (80 mL) and saturated NaCl (80 mL) and then dried (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) gave a light yellow oil **47b** (8.99 g, 98.2%) which was placed on a vacuum pump overnight (RT/0.2 mm Hg). IR (film) 3090, 3010, 3005 (ArH), 2920, 2780 (C-H), 735, 700 (C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.14 [m, 2 H, $(CH_2)_{ax}$, cyclopropyl ring], 0.51 [m, 2 H, $(CH_2)_{eq}$, cyclopropyl ring], 0.94 [m, 1 H, (*CH*), cyclopropyl ring], 1.52 [dd, J = 19.8 Hz, 2 H, H(9)], 1.91 [m, 2 H, H(1,5)], 2.20 (d, J = 6.6 Hz, 2 H, CH_2-cyclopropyl), 2.33 [dd, J = 10.7 Hz, J = 3.6 Hz, 2 H, $H(6,8)_{ax}$], 2.41 [dd, J = 10.8 Hz, J = 4.8 Hz, 2 H, $H(2,4)_{ax}$], 2.76 [d, J = 10.5 Hz, 2 H, $H(6,8)_{eq}$], 2.85 [d, J = 10.5 Hz, 2 H, $H(2,4)_{eq}$], 3.49 (s, 2 H, Ar-CH_2), 7.21-7.45 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.90 (CH_2, cyclopropyl ring), 8.72 (*C*H, cyclopropyl ring), 29.43 [C(9)], 30.22 [C(1,5)], 57.68 [C(2,4)], 57.90 [C(6,8)], 62.75 (Ar-CH_2), 64.04 (CH_2-cyclopropyl), 126.38, 127.92, 128.62, 139.74 (Ar-*C*). IR and ^{13}C NMR spectra confirmed the absence of the ketone carbonyl, and thus the oil was used without further purification to prepare salt **37** and secondary amine **47c**.

3-Cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonane (47c). A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with N_2 inlet, and two glass stoppers. The flask was initially flushed with N_2 for a period of 15 min. Palladium-on-carbon (Alfa, 10%, 0.997 g, 30 mg of catalyst/mmol of the amine) was added in one portion, and the system was flushed with N_2. Dry and deoxygenated H_3COH (90 mL) was slowly poured over the catalyst (CAUTION: catalyst can ignite in the presence of air). To the stirred solution were added amine **47b** (8.99 g, 33.24 mmol) and anhydrous HCO_2NH_4 (5.24 g, 83.1 mmol), and the resulting mixture was boiled under N_2 for 30 min. Cooling the mixture to RT, and

filtering through a celite pad, was followed by concentration (rotary evaporator) of the resulting solution to give an off-white, viscous oil. The oil was then dissolved in H_2O (100 mL) and made basic (pH~12) using 10% NaOH pellets. Combined extracts (CCl_4, 4 x 60 mL) of the aqueous solution were dried (Na_2SO_4, 1 h), filtered (gravity) and concentrated (rotary evaporator) to give a yellow oil **47c** (5.50 g, 91.8%); IR (film) 3300 (N-H), 3090, 3010 (C*H*$_2$ cyclopropyl), 2900, 2860, 2780 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.13 [m, 2 H, (C*H*$_2$)$_{ax}$, cyclopropyl ring], 0.52 [m, 2 H, (C*H*$_2$)$_{eq}$, cyclopropyl ring], 0.87 [m, 1 H, (C*H*), cyclopropyl ring], 1.64 [m, 2 H, H(1,5)], 1.82 [m, 2 H, H(9)], 2.07 (d, J = 6.6 Hz, 2 H, C*H*$_2$-cyclopropyl), 2.31 [d, J = 11.1 Hz, 2 H, H(6,8)$_{ax}$], 2.94 [d, J = 13.8 Hz, 2 H, H(2,4)$_{ax}$], 3.09 [d, J = 13.2 Hz, 2 H, H(6,8)$_{eq}$], 3.17 [d, J = 11.1 Hz, 2 H, H(2,4)$_{eq}$], 4.09 [bs, 1 H, (N-*H*)]; ^{13}C NMR ($DCCl_3$) ppm 3.76 (*C*H$_2$, cyclopropyl ring), 8.76 (*C*H, cyclopropyl ring), 29.87 [C(9)], 33.23 [C(1,5)], 52.45 [C(6,8)], 59.51 [C(2,4)], 64.32 (*C*H$_2$-cyclopropyl). The ^1H NMR spectrum was void of aromatic protons , and thus the oil was used without further purification to prepare amides **39** and **50**.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (48). A 250-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C, ice bath) solution of amine **47a** (3.4 g, 16.16 mmol) in dry ether (50 ml) was added $HClO_4$ (60%, 3.4 g , 20.2 mmol) dropwise over a period of 15 min. The mixture was allowed to stir an additional 15 min at 0-5°C. A white precipitate formed and was filtered and washed with cold ether (30 mL). The solid was recrystallized (H_3COH, 30 mL), and white needles were collected, washed with cold H_3COH (25 mL), and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 3.63 g (72.3%) of salt **48**; mp 211-212°C. IR (KBr) 3560 (O-H), 3400 (N-H), 2985, 2940, 2850 (C-H), 1090 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.14 (d, J = 6.2 Hz, 12 H, C*H*$_3$ isopropyl), 1.80 [bs, 2 H, H(1,5)], 2.21 [bs, 2 H, H(9)], 2.97 (d, J = 11.9 Hz, 4 H, ring protons), 3.19 (m, 2 H, C-*H* isopropyl), 3.28 (d, J

= 12.2 Hz, 4 H, ring protons); ^{13}C NMR (D_3CCN) ppm 17.11 (CH_3 isopropyl), 28.56 [C(1,5)], 31.41 [C(9)], 54.26 [C(2,4 6,8)], 56.13 (*C*-H isopropyl). Mass spectral (EI) data calcd for $C_{13}H_{27}N_2O_4Cl$ *m/z* (M+): 210.2096. Found: 210.2096. Anal. Calcd for $C_{13}H_{27}N_2O_4Cl$: C, 50.24; H, 8.76; N, 9.01. Anal. Calcd for $C_{13}H_{27}N_2O_4Cl \cdot 0.2\ H_2O$: C, 49.66; H, 8.78; N, 8.91. Found: C, 49.33; H, 8.52; N, 9.31.

3,7-Diisopropyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (49a). A 250-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser with a N_2 inlet, a Dean-Stark trap, and a heating mantle. After addition of ketone **46a** (8.0 g, 35.66 mmol), 1,2-ethanedithiol (33.59 g, 356.6 mmol), *p*-toluene-sulfonic acid (16.28 g, 85.58 mmol) and benzene (200 mL), the resulting mixture was heated at reflux for 40 h. The solvent (benzene) was then removed through a Dean-Stark trap, and the resulting oil was dissolved in H_2O (100 mL) and transferred to a separatory funnel. The aqueous layer was extracted (ether, 2 x 100 mL), the extracts being discarded. Basification (pH~12) was achieved using 10% NaOH followed by extraction (ether, 4 x 75 mL) and washing with NaOH (1 *N*, 90 mL) and brine (90 mL). After drying (Na_2SO_4, 2 h) the solution, evaporation (rotary evaporator) afforded 8.06 g (75.2%) of a light yellow oil **49a**; IR (film) 2905, 2800 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.03 (d, J = 12.5 Hz, 12 H, CH_3 isopropyl), 2.26 [bs, 2 H, H(1,5)], 2.62 (d, 4 H, ring protons), 2.77 (m, 2 H, C-*H* isopropyl), 2.89 (d, J = 12.7 Hz, 4 H, ring protons), 3.08 (s, 4 H, S-CH_2); ^{13}C NMR ($DCCl_3$) ppm 17.97 (CH_3 isopropyl), 37.39 [C(1,5)], 43.11 (S-CH_2), 51.20 [C(2,4,6,8)], 53.21 (*C*-H isopropyl), 70.89 [C(9)]. Spectral analysis (IR and ^{13}C) of the oil did not show the presence of a carbonyl group as present in **46a**, and thus the thioketal was used without purification to prepare **38**.

7-Benzyl-3-cyclopropylmethyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]-nonane (49b). A 250-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser with a N_2 inlet, a Dean-Stark trap, and a heating mantle. After addition of ketone **46b** (6.0 g, 21.09 mmol), 1,2-ethanedithiol (19.87 g, 210.9 mmol), *p*-toluene-sulfonic acid (9.63 g, 50.6 mmol) and benzene (120 mL), the resulting mixture was heated at reflux for 30 h. The solvent (benzene) was removed through a Dean-Stark trap, and the resulting oil was dissolved in H_2O (100 mL). The aqueous layer was extracted (ether, 2 x 50 mL), and these extracts were discarded. Basification of the aqueous solution (pH~12) was achieved using an aqueous 10% NaOH solution. This new solution was extracted (ether, 4 x 75 mL), and the extracts were then washed with NaOH (1 *N*, 90 mL) and saturated NaCl (90 mL). After drying (Na_2SO_4, 2 h), the organic solution was evaporated (rotary evaporator) to afford 6.44 g (84.7%) of **49b**, a light yellow oil; IR (film) 3080, 3010, 3000 (ArH), 2905, 2800 (C-H), 730, 705 (C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.14 [m, 2 H, $(CH_2)_{ax}$, cyclopropyl ring], 0.51 [m, 2 H, $(CH_2)_{eq}$, cyclopropyl ring], 0.92 [m, 1 H, (*CH*), cyclopropyl ring], 2.15 [m, 2 H, H(1,5)], 2.27 (d, J = 5.5 Hz, 2 H, CH_2-cyclopropyl), 2.73-2.84 (m, 8 H, ring protons), 3.14 (s, 4 H, SCH_2), 3.53 (s, 2 H, Ar-CH_2), 7.24-7.46 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.83 (CH_2, cyclopropyl ring), 8.60 (*C*H, cyclopropyl ring), 37.93, 37.98 [C(1,5)], 43.51 (SCH_2), 56.56 [C(2,4)], 56.67 [C(6,8)], 61.68 (CH_2-Ar), 62.49 (CH_2-cyclopropyl), 71.91 [C(9)], 126.60, 128.02, 128.62, 139.34 (Ar-*C*). Thioketal **49b** was used without further purification to prepare salt **43**.

3-Benzoyl-7-cyclopropylmethyl-3,7-diazabicyclo-[3.3.1]nonane (50). Into a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, 25-mL addition funnel, a condenser with N_2 inlet, and a glass stopper were placed the amine **47c** (5.50 g, 30.51 mmol) and NaOH (10%, 30.60 g, 76.28 mmol) in H_2CCl_2 (25 mL). A

solution of benzoyl chloride (4.72 g, 33.56 mmol) in H_2CCl_2 (15 mL) was added dropwise over a period of 0.5 h under N_2. The mixture was allowed to stir an additional 3 h. Addition of H_2O (50 mL) was followed by extraction with H_2CCl_2 (3 x 50 mL). Combined extracts were dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator) to give a yellow oil. Flash chromatography of the oil was performed on neutral alumina (50 g, 60-mL fritted funnel, suction) with ethyl acetate as the eluent. The filtrate was concentrated (rotary evaporator) and placed on a vacuum pump overnight (RT/0.2 mm Hg) to give 7.15 g (82.4%) of amide **50** as an oil. IR (film) 3090, 3005 (Ar-H), 2920, 2860, 2775 (C-H), 1630 (NC=O), 715 (C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.11 [bd, 2 H, cyclopropyl $CH_{2\,(ax)}$], 0.49 [m, 2 H, cyclopropyl $CH_{2\,(eq)}$], 0.92 (m, 2 H, cyclopropyl C-*H*), 1.74 [m, 3 H, H(5,9)], 1.98 [bs, 2 H, H(1), CH_2 cyclopropyl], 2.23 [bs, 3 H, $H(4,6)_{ax}$, CH_2 cyclopropyl], 2.94 [d, 1 H, $H(6)_{eq}$], 3.01 [d, 1 H, $H(2)_{ax}$], 3.28 [m, 2 H, $H(8)_{ax}$, $H(4)_{eq}$], 3.78 [d, J = 12.2 Hz, 1 H, $H(8)_{eq}$], 4.79 [d, J = 12.1 Hz, 1 H, $H(2)_{eq}$], 7.38 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 2.85, 4.11 (cyclopropyl CH_2), 7.95 (cyclopropyl *C*-H), 28.64, 29.01 [C(1,5)], 31.72 [C(9)], 46.02 [C(2)], 51.74, 57.71, 57.98 [C(4,6,8)], 63.84 (CH_2 cyclopropyl), 126.13, 127.64, 128.07, 137.20 (Ar-*C*), 169.68 (N*C*=O). Benzamide **50** was used without further purification to prepare salt **42**.

3-(4-Chlorobenzoyl)-7-methylcyclopropyl-3,7-diaza-bicyclo[3.3.1]nonane Hydroperchlorate (51). A 125-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath. To a chilled (5°C, via ice bath) solution of amide **39** (1.0 g, 3.14 mmol) in ether (30 mL) was added $HClO_4$ (60%, 0.66 g, 3.92 mmol) dropwise over a period of 15 min. The suspension was stirred an additional 10 min at this temperature followed by filtration. This white solid was recrystallized from H_3COH (25 mL) which was followed by filtration and drying (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 0.93 g (70.9 %) as

white needles of **51**; mp 231-232°C. IR (KBr) 3180 (N-H), 3095, 3020 (Ar-H), 2950, 2880 (C-H), 1620 (NC=O), 1090 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 0.51 [d, J = 3.2 Hz, 2 H, (CH_2)$_{ax}$ cyclopropyl ring], 0.82 [d, J = 3.6 Hz, 2 H, (CH_2)$_{eq}$ cyclopropyl ring], 1.18 (m, 1 H, C-*H* cyclopropyl), 1.85 [bd, 1 H, H(9)], 2.33 [bs, 3 H, H(1,5,9)], 3.03 (d, J = 6.2 Hz, 2 H, CH_2 cyclopropyl), 3.29 (m, 4 H, ring protons), 3.74 (bs, 2 H, ring protons), 4.09 (bs, 2 H, ring protons), 7.36 (d, 2 H, Ar-*H*), 7.48 (d, 2 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 4.94, 6.40 (cyclopropyl CH_2), 27.89 [C(1,5)], 29.05 [C(9)], 57.42, 63.98, 64.08 [C(2,4,6,8), CH_2-cyclopropyl], 118.37, 129.67, 129.79, 129.95, 135.08, 136.29 (Ar-*C*), 173.85 (N*C*=O); Mass spectral (EI) data calcd for $C_{18}H_{24}Cl_2N_2O_5$ *m/z* (M+): 318.1499 (-$HClO_4$). Found: 318.1500. Anal. calcd for $C_{18}H_{24}Cl_2N_2O_5$: C, 51.56; H, 5.77. Found: C, 51.34; H, 5.85.

3-(4-Nitrobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52a). To a 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with N_2 inlet, a 25-mL addition funnel and two glass stoppers. To a mixture of amine **52j** (3.82 g, 22.70 mmol) in H_2CCl_2 (25 mL) and 10% NaOH (22.76 g, 56.80 mmol) was added dropwise 4-nitrobenzoyl chloride (4.63 g, 24.90 mmol) in H_2CCl_2 (15 mL) over a period of 15 min. Stirring (magnetic) of the mixture was continued for an additional 3 h under N_2. To the heterogenous mixture was added H_2O (100 mL) in one portion and, after transferring the mixture to a separatory funnel, the two layers were separated. Further extracts (H_2CCl_2, 3 x 50 mL) of the aqueous layer were combined, dried (Na_2SO_4, 1 h), filtered and concentrated (rotary evaporator) to give a viscous yellow oil which solidified upon standing. This yellow solid was dissolved in ether, and the solution was gravity filtered. The filtrate was concentrated (rotary evaporator) and then placed on vacuum pump overnight (RT/0.2 mm Hg) to give 6.79 g (94.3 %) of a light yellow solid **52a**; mp 119-120°C. IR (KBr) 3090, 3005 (Ar-H), 2920, 2880, 2770 (C-H), 1635 (NC=O), 760 (C-H out of plane, para) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.56 (d,J =

6.7 Hz, 3 H, C*H*$_3$ isopropyl), 0.69 (d, J = 6.7 Hz, 3 H, C*H*$_3$ isopropyl), 1.34 [m, 2 H, H(9)$_{ax}$, H(5)], 1.61 [bs, 1 H, H(1)], 2.04-2.32 [m, 3 H, ring protons], 2.67 (dd, J = 11.2 Hz, 2 H, ring protons), 2.94 (dd, J = 12.9 Hz, 1 H, ring proton), 3.20 (d, J = 12.9 Hz, 1 H, ring proton), 3.39 (d, J = 11.2 Hz, 1 H, ring proton), 7.13 (d, 2 H, Ar-*H*), 7.85 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 15.89, 19.46 (*C*H$_3$ isopropyl), 28.81 29.57 [C(1,5)], 32.04 [C(9)], 46.55 [C(2)], 51.79, 52.31, 54.26, 54.85 [C(4,6,8), *C*-H isopropyl], 123.52, 127.60, 143.91, 147.62 (Ar-*C*), 167.58 (N*C*=O); Mass spectral (EI) data calcd for $C_{17}H_{23}N_3O_3$ *m/z* (M^+): 317.1739. Found: 317.1750; Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.06; H, 7.36; N, 12.97.

3-[(4-N-Acetyl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52b). In a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, 25-mL addition funnel, a condenser with N_2 inlet and a glass stopper were placed amide **44** (3.50 g, 12.2 mmol) and NaOH (10%, 12.2 g, 30.50 mmol) in H_2CCl_2 (25 mL). A solution of acetyl chloride (1.05 g, 13.4 mmol) in H_2CCl_2 (10 mL) was added dropwise over a period of 0.5 h under N_2. The mixture was allowed to stir for an additional 3 h. Addition of H_2O (50 mL) was followed by separating the two layers. The organic phase was further extracted (H_2CCl_2, 3 x 40 mL), and the combined extracts were dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator) to give a light yellow oil. Flash chromatography of the oil was performed on neutral alumina (50 g, 60-mL fritted funnel, suction) with ethyl acetate as the eluent. The filtrate was concentrated (rotary evaporator) and placed on a vacuum pump overnight (RT/0.2 mm Hg) to give 3.44 g (85.5%) of amide **52b** as a white solid; mp 77-78°C. IR (KBr) 3280 (N-H), 3100, 3060 (Ar-H), 2980, 2940, 2800 (C-H), 1690 (NHC(O)CH_3), 1615 (NC=O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.94 (d, J = 6.2 Hz, 3 H, C*H*$_3$ isopropyl), 1.03 (d, J = 6.2 Hz, 3 H, C*H*$_3$ isopropyl), 1.67 [bd, 1 H, H(9)$_{ax}$], 1.74 [bd, 1 H, H(9)$_{eq}$], 1.96 [bs, 2 H, H(1,5)], 2.11 [s, 3 H,

NHC(O)C*H*$_3$], 2.42 (d, J = 10.1 Hz, 1 H, ring proton), 2.48 (d, J = 10.1 Hz, 1 H, ring proton), 2.56 (m, 1 H, C-*H* isopropyl), 2.71 (d, J = 10.9 Hz, 1 H, ring proton), 3.04 (m, 1 H, ring proton), 3.30 (d, J = 12.8 Hz, 1 H, ring proton), 3.79 (d, J = 12.8 Hz, 1 H, ring proton), 4.76 (d, J = 12.8 Hz, 1 H, ring proton), 7.17 (d, 2 H, Ar-*H*), 7.36 (d, 2 H, Ar-*H*), 9.24 (bs, 1 H, N-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.29, 19.24 (*C*H$_3$ isopropyl), 24.09 [NHC(O)*C*H$_3$], 29.05, 29.65 [C(1,5)], 32.20 [C(9)], 46.70 [C(2)], 52.24, 52.85, 54.24, 54.63 [C(4,6,8), *C*-H isopropyl], 119.96, 127.19, 132.29, 139.12 (Ar-*C*), 169.34 [NH*C*(O)CH$_3$], 170.19 (N*C*=O). Benzamide **52b** was used without further purification to prepare hydro-perchlorate **53a**.

3-[4-(Methylsulfonyl)amino]benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52c). A 100-mL, three-necked, round-bottomed flask was equipped with a 25-mL addition funnel, magnetic stirrer, condenser with N_2 inlet, and an ice bath. To a chilled (5°C) solution of amide **44** (3.0 g, 10.44 mmol) and pyridine (0.87 g, 10.96 mmol) in H_2CCl_2 (20 mL) was added dropwise methanesulfonyl chloride (1.18 g, 10.34 mmol) in H_2CCl_2 (10 mL) over a 15 min period. When the addition was completed, the mixture was allowed to stir at RT overnight. Suction filtration of the mixture removed traces of pyridine hydrochloride, and the filtrate was transferred to a separatory funnel. Extraction (1 *N* NaOH, 4 x 40 mL) was followed by neutralization (pH~7) of the aqueous phase using acetic acid, and the remaining organic layer was discarded. This neutral solution was extracted (H_2CCl_2, 4 x 40 mL), dried (Na_2SO_4, 2 h) and filtered. After concentration (rotary evaporator), there was obtained 3.46 g (90.6%) of an off-white solid **52c**; mp 89-91°C. IR (KBr) 3140 (N-H), 3040 (Ar-H), 2980, 2930, 2870, 2810 (C-H), 1610 (NC=O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.97 (d, J = 6.1 Hz, 3 H, C*H*$_3$ isopropyl), 1.08 (d, J = 6.1 Hz, 3 H, C*H*$_3$ isopropyl), 1.69 [bs, 1 H, H(5)], 1.79 [bd, 2 H, H(9)], 1.98 [bs, 1 H, H(1)], 2.42 (d, J = 11.3 Hz, 1 H, ring proton), 2.51 (d, J = 11.3 Hz, 1 H, ring proton),

2.60 (m, 1 H, C-*H* isopropyl), 2.74 (d, J = 11.3 Hz, 1 H, ring proton), 3.03 (m, 5 H, ring protons, SO_2CH_3), 3.32 (d, J = 13.0 Hz, 1 H, ring proton), 3.78 (d, J = 13.0 Hz, 1 H, ring proton), 4.76 (d, J = 13.0 Hz, 1 H, ring proton), 7.21-7.30 (q, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.26, 1916 (CH_3 isopropyl), 28.89, 29.55 [C(1,5)], 32.05 [C(9)], 39.18 (SO_2CH_3), 46.76 [C(2)], 52.11, 52.52, 54.19, 54.54 [C(4,6,8), *C*-H isopropyl], 119.80, 128.05, 128.16, 133.22, 138.21 (Ar-*C*), 169.63 (N*C*=O). Sulfonamide **52c** was used without further purification to prepare salts **41** and **54c**.

3-(4-Fluorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52d). In a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, 25-mL addition funnel, a condenser with N_2 inlet and a glass stopper were placed amine **52j** (2.53 g, 15.03 mmol) and NaOH (10%, 15.07 g, 37.58 mmol) in H_2CCl_2 (25 mL). A solution of 4-fluorobenzoyl chloride (2.62 g, 16.54 mmol) in H_2CCl_2 (15 mL) was added dropwise over a period of 0.5 h under N_2. The mixture was allowed to stir an additional 3 h. Addition of H_2O (50 mL) was followed by extraction with H_2CCl_2 (3 x 50 mL). Combined extracts were dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator) to give a light yellow oil. Flash chromatography of the oil was performed on neutral alumina (50 g, 60-mL fritted funnel, suction) with hexane:ethyl acetate (60:40) as the eluent. The filtrate was concentrated (rotary evaporator) and placed on a vacuum pump overnight (RT/0.2 mm Hg) to give 3.88 g (89.0%) of amide **52d** as a white solid; mp 87-88°C. IR (KBr) 3090, 3005 (Ar-H), 2975, 2930, 2860 (C-H), 1630 (NC=O), 750 (C-H out of plane, mono) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.96 (d, J = 5.9 Hz, 3 H, CH_3 isopropyl), 1.07 (d, J = 5.9 Hz, 3 H, CH_3 isopropyl), 1.71 [m, 3 H, H(9), H(5)], 1.95 [s, 1 H, H(1)], 2.41-2.72 (m, 4 H, ring protons, C-H isopropyl), 3.03 (d, J = 12.7 Hz, 2 H, ring protons), 3.31 (d, J = 12.7 Hz, 1 H, ring proton), 3.72 (d, J = 12.7 Hz, 1 H, ring proton), 4.74 (d, J = 12.7 Hz, 1 H, ring proton), 7.08 (m, 2 H, Ar-*H*), 7.36 (m, 2 H, Ar-*H*); ^{13}C

NMR ($DCCl_3$) ppm 16.26, 19.18 (CH_3 isopropyl), 28.97, 29.69 [C(1,5)], 32.16 [C(9)], 46.59 [C(2)], 52.12, 52.49, 54.65 [C(4,6,8), *C*-H isopropyl], 114.96, 115.25, 128.77, 128.88, 133.60, 133.64 (Ar-*C*), 161.04, 164.33 (J = 248.2 Hz, Ar*C*-F), 169.07 (N*C*=O); ^{15}N NMR ($DCCl_3$) ppm 40.78 [N(7)], 119.65 [N(3)]; Mass spectral (EI) data calcd for $C_{17}H_{23}N_2OF$ *m/z* (M^+): 290.1794. Found: 290.1790. Anal. Calcd for $C_{17}H_{23}N_2OF$: C, 70.32; H, 7.98; N, 9.65. Found: C, 70.39; H, 8.03; N, 9.71.

3-[4-(1H-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52e). A 200-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with N_2 inlet and two glass stoppers. To a solution of amide **52d** (3.35 g, 11.54 mmol) in DMSO (15 mL) was added imidazole (1.18 g, 17.30 mmol), potassium carbonate (anhydrous,1.67 g, 12.12 mmol), and 18-crown-6 (100 mg). The stirred mixture was heated at 110°C for 45 h under N_2 via the use of boiling toluene (bp 110°C) in the jacket. Cooling the solution to RT was followed by the addition of chilled H_2O (75 mL). Combined extracts (H_2CCl_2, 4 x 40 mL) of the suspension were washed with H_2O (80 mL) and satd NaCl (80 mL); the solution was then dried (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) gave a light yellow solid [which was placed on a vacuum pump overnight (RT/0.2mm Hg)]. Flash chromatography (neutral alumina) of the crude solid in solution using ethyl acetate:hexane (2:3) caused the starting material to be eluted first. With a more polar solvent system [EtOAc:H_3COH (30:1)], product **52e** could be isolated (1.35 g, 35.1%) as an off white solid. This solid was sensitive to air and became gummy when exposed to the atmosphere. IR(film) 3400 (N-H), 3110 (Ar-H), 2975, 2910, 2800 (C-H), 1620 (NC=O), 735 (para) cm^{-1}; ^1H ($DCCl_3$) δ 0.96-1.14 (dd, J = 5.9 Hz, 6 H, CH_3 isopropyl), 1.68 [bd, 1 H, H(9)], 1.81 [bs, 2 H, H(1,5)], 2.02 [bs, 1 H, H(9)], 2.45 (d, J = 10.8 Hz, 1 H, ring proton), 2.57 (d, J = 10.8 Hz, 1 H, ring proton), 2.63 (m, 1 H, C-*H* isopropyl),

2.77 (d, J = 10.8 Hz, 1 H, ring proton), 3.09 (d, J = 12.4 Hz, 2 H, ring protons), 3.38 (d, J = 12.4 Hz, 1 H, ring proton), 3.76 (d, J = 12.4 Hz, 1 H, ring proton), 4.79 (d, J = 12.4 Hz, 1 H, ring proton), 7.22 (s, 1 H, C-*H* imidazole), 7.32 (s, 1 H, C-*H* imidazole), 7.41-7.54 (dd, 4 H, Ar-*H*), 7.89 (s, 1 H, C-*H* imidazole); ^{13}C NMR ($DCCl_3$) ppm 16.33, 19.41 (*C*H_3 isopropyl), 29.03, 29.78 [C(1,5)], 32.26 [C(9)], 46.72 [C(2)], 52.15, 52.61, 54.38, 54.82 [C(4,6,8), *C*-H isopropyl], 118.07 (*C*-H imidazole), 121.15, 128.54 (Ar-C), 130.60, 135.44 (*C*-H imidazole), 136.91, 137.43 (Ar-*C*), 168.80 (N*C*=O). Because of it's hygroscopic nature, benzamide **52e** was converted directly to the hydroperchlorate **53c**.

3-[4-(Nitro)phenylacetyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52f). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a 25-mL addition funnel, a condenser with a N_2 inlet, and one glass stopper. Initially, the amine **52j** (2.42 g, 14.38 mmol) in H_2CCl_2 (35 mL) was added followed by NaOH (10%, 14.42 g, 35.95 mmol) which resulted in formation of a heterogenous mixture. To this mixture was added dropwise 4-nitrophenylacetyl chloride (**65**, 3,16 g, 15.82 mmol) over a 15-min period. Stirring was continued for an additional 3 h after which the brown mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted (H_2CCl_2, 3 x 25 mL), and the organic layers were combined. After drying (Na_2SO_4, 2 h), the organic solution was filtered and concentrated (rotary evaporater) to give **52f** as a light brown solid (3.3 g, 69.2 %); mp 93-94°C. IR (KBr) 3090 (Ar-H), 2960, 2920, 2800, 2740 (C-H), 1625 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.94 (dd, J = 6.4 Hz, 6 H, C*H*$_3$ isopropyl), 1.69 [q, 2 H, H(9)], 1.92 [bs, 2 H, H(1,5)], 2.46 [m, 3 H, ring protons, C-*H* isopropyl), 2.79 (d, J = 11.2 Hz, 1 H, ring proton), 2.93 (m, 2 H, ring protons), 3.39 (d, J = 13.2 Hz, 1 H, ring proton), 3.79 (s, 2 H, C*H*$_2$-Ar), 3.84 (d, J = 13.2 Hz, 1 H, ring proton), 4.57 (d, 1 H, ring proton), 7.44 (d, 2 H, Ar-*H*), 8.15 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.83, 18.44 (*C*H_3 isopropyl), 28.76, 29.42 [C(1,5)],

31.57 [C(9)], 40.62 (CH_2-Ar), 46.76 [C(2)], 50.60, 52.78, 54.03, 54.42 [C(4,6,8), *C*-H isopropyl], 123.37, 130.02, 143.58, 146.56 (Ar-*C*), 167.93 (N*C*=O). Amide **52f** was used without further purification to prepare **52g** and **53d**.

3-[4-(Amino)phenylacetyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52g). To a 500-mL, Erlenmeyer flask equipped with a magnetic stirrer was added amide **52f** (5.4 g, 16.3 mmol) in AcOH/H_2O (1:1, 80 mL). After obtaining a homogenous solution, $TiCl_3$ (12%, 135.3 g, 114.1 mmol) was added in one portion, and this purple solution was stirred at room temperature for 7 min. Upon cooling (ice bath, 5°C) the reaction mixture, 20% NaOH was added slowly until a dark blue color persisted (pH~12). Extraction ($HCCl_3$, 3 x 100 mL) was followed by washing of the organic layer with H_2O (150 mL) and satd NaCl (150 mL). The organic layer was dried (Na_2SO_4, 3 h), filtered, and concentrated (rotary evaperator) which gave **52g** (4.03 g, 82.1%) as a light yellow, viscous oil. IR (film) 3350, 3240 (N-H), 3040 (Ar-H), 2980, 2930, 2800 (C-H), 1630 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.93 (dd, J = 6.5 Hz, 6 H, C*H*$_3$ isopropyl), 1.61 [q, 2 H, H(9)], 1.82 [bd, 2 H, H(1,5)], 2.32-2.49 (m, 3 H, ring protons, C-*H* isopropyl), 2.71 (d, J = 11.5 Hz, 1 H, ring proton), 2.86 (d, J = 11.5 Hz, 1 H, ring proton), 2.92 (d, J = 11.5 Hz, 1 H, ring proton), 3.25 (d, J = 11.5 Hz, 1 H, ring proton), 3.58 (q, 2 H, Ar-C*H*$_2$), 3.69 (bs, 2 H, N*H*$_2$), 3.83 (d, J = 13.0 Hz, 1 H, ring proton), 4.51 (d, J = 13.0 Hz, 1 H, ring proton), 6.58 (d, 2 H, Ar-*H*), 7.01 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.48, 18.06 (*C*H$_3$ isopropyl), 28.46, 29.01 [C(1,5)], 31.15 [C(9)], 40.20 (Ar-*C*H$_2$), 46.14 [C(2)], 50.13, 52.52, 53.51, 53.89 [C(4,6,8), *C*-H isopropyl], 114.75, 125.58, 129.04, 144.71 (Ar-*C*), 169.80 (N*C*=O). Amide **52g** was used directly without further purification to prepare sulfonamide **52i**.

3-[4-(*N*-Acetyl)phenylacetyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52h). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with N_2 inlet, a 25-mL addition funnel and two glass stoppers. To a mixture of amide **52g** (2.0 g, 6.63 mmol) in H_2CCl_2 (25 mL) and 10% NaOH (6.65 g, 16.58 mmol) was added dropwise a solution of acetyl chloride (0.57 g, 7.30 mmol) in H_2CCl_2 (5 mL) over a period of 15 min. Stirring (magnetic) of the mixture was continued for an additional 3 h under N_2. To the heterogenous mixture was added H_2O (100 mL) and the two layers were separated. Further extracts (H_2CCl_2, 3 x 30 mL) of the aqueous layers were combined and dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator). The resulting oil was placed on a vacuum pump overnight (RT/0.2 mm Hg) to give 2.03 g (89.1 %) of **52h** as an light yellow solid; mp 71-72°C. IR (KBr) 3300 (N-H), 3080, 3050 (Ar-H), 2980, 2930, 2870, 2800 (C-H), 1680 [NC(O)CH_3], 1620 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.94 (dd, J = 6.0 Hz, 6 H, C*H*$_3$ isopropyl), 1.68 [bd, 2 H, H(9)], 2.11 [s, 3 H, C*H*$_3$C(O)], 2.40 (d, J = 11.6 Hz, 1 H, ring proton), 2.49 (m, 2 H, ring proton, C-*H* isopropyl), 2.78 (d, J = 11.6 Hz, 1 H, ring proton), 2.87 (d, J = 11.6 Hz, 1 H ring proton), 2.96 (d, J = 11.6 Hz, 1 H, ring proton), 3.32 (d, J = 13.1 Hz, 1 H, ring proton), 3.64 (m, 2 H, Ar-C*H*$_2$), 3.87 (d, J = 13.1 Hz, 1 H, ring proton), 4.55 (d, J = 13.1 Hz, 1 H, ring proton), 7.08 (d, 2 H, Ar-*H*), 7.36 (d, 2 H, Ar-*H*), 8.70 (s, 1 H, N-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.99, 18.33 (*C*H$_3$ isopropyl), 24.13 [*C*H$_3$C(O)], 28.83, 29.39 [C(1,5)], 31.55 [C(9)], 40.49 (Ar-*C*H$_2$), 46.75 [C(2)], 50.62, 53.02, 53.99, 54.28 [C(4,6,8), *C*-H isopropyl], 120.28, 129.06, 130.73, 136.86 (Ar-*C*), 168.89 [NH*C*(O)CH_3], 169.94 (N*C*=O). Amide **52h** was used directly to prepare hydroperchlorate **53e**.

3-[4-(Methylsulfonyl)amino]phenylacetyl-7-isopropyl-3,7-diazabicyclo[3.3.1]-nonane (52i). A 100-mL, three-necked, round-bottomed flask was equipped with a 25-mL addition funnel, magnetic stirrer, condenser with N_2 inlet, and an ice bath. To a

chilled (5°C) solution of amide 52g (2.1 g, 6.97 mmol) and pyridine (0.58 g, 7.32 mmol) in H_2CCl_2 (20 mL) was added dropwise methanesulfonyl chloride (0.79 g, 6.90 mmol) in H_2CCl_2 (10 mL) over a 15 min period. After the addition was complete, the mixture stirred at RT overnight. Filtration (suction) of the mixture removed traces of pyridine hydrochloride, and the filtrate was transferred to a separatory funnel. Extraction (1 *N* NaOH, 4 x 40 mL) was followed by neutralization (pH~7) of the aqueous phase using acetic acid, and the remaining organic layer was discarded. This neutral solution was extracted (H_2CCl_2, 4 x 40 mL), dried (Na_2SO_4, 2 h) and filtered. After concentration (rotary evaporator), sulfonamide **52i** was obtained 2.32 g (87.4%) as an off-white solid; mp 73-74°C. IR (KBr) 3140 (N-H), 3050 (Ar-H), 2980, 2920, 2880, 2800 (C-H), 1630 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.94 (dd, J = 5.9 Hz, 6 H, C*H*$_3$ isopropyl), 1.69 [m, 2 H, H(9)], 1.93 [bs, 2 H, H(1,5)], 2.41 (bd, 1 H, ring proton), 2.52 (m, 2 H, ring proton, C-*H* isopropyl), 2.84 (d, J = 11.0 Hz, 1 H, ring proton), 2.93 (m, 6 H, ring protons, SO_2CH_3), 3.38 (d, J = 11.0 Hz, 1 H, ring proton), 3.66 (s, 2 H, Ar-C*H*$_2$), 3.90 (d, J = 12.9 Hz, 1 H, ring proton), 4.59 (d, J = 12.9 Hz, 1 H, ring proton), 7.11 (dd, 4 H, Ar-*H*), 7.37 (s, 1 H, SO_2N-*H*); ^{13}C NMR ($DCCl_3$) ppm 17.17, 18.31 (*C*H$_3$ isopropyl), 28.84, 29.47 [C(1,5)], 31.62 [C(9)], 38.76 (SO_2CH_3), 40.05 (Ar-*C*H$_2$), 46.89 [C(2)], 50.58, 53.04, 54.07, 54.30 [C(4,6,8), *C*-H isopropyl], 121.66, 130.13, 132.44, 135.68 (Ar-*C*), 169.77 (N*C*=O). Amide **52i** was used without further purification to prepare hydroperchlorate **53f**.

3-[(4-*N*-Acetyl)benzoyl]-7-isopropyl-3,7-diazabicyclo-[3.3.1]nonane Hydroperchlorate (53a). A 125-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C) solution of amide **52b** (1.78 g, 5.40 mmol) in ether (25 mL) was added dropwise a solution of $HClO_4$ (60%, 1.13 g, 6.75 mmol) in ether (5 mL) over a period of 5 minutes. After stirring an additional 15 min at 5°C, the white precipitate was filtered and washed with cold ether. Recrystallization (H_3COH, 15 mL) of the

precipitate gave a new solid which was filtered and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 1.03 g (76.3%) of salt **53a** as white platelettes; mp 166-167°C. IR (KBr) 3555 (O-H), 3360 (N-H), 3140 (N-H), 3020 (Ar-H), 2940, 2880 (C-H), 1690 [NHC(O)CH_3], 1630 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.38 (d, J = 6.1 Hz, 6 H, C*H*$_3$ isopropyl), 1.82 [bd, 2 H, H(9)], 2.12 [s, 3 H, NHC(O)C*H*$_3$], 2.33 [bs, 2 H, H(1,5)], 3.16 (bd, 2 H, ring protons), 3.29 (m, 2 H, ring protons), 3.55 (bd, 3 H, ring protons, C-*H* isopropyl), 4.10 (d, J = 13.1 Hz, 2 H, ring protons), 7.22 (d, 2 H, Ar-*H*), 7.57 (d, 2 H, Ar-*H*), 8.61 (bs, 1 H, N-*H*); ^{13}C NMR (D_3CCN) ppm 16.90 (bs, *C*H$_3$ isopropyl), 24.46 [NHC(O)*C*H$_3$], 28.01 [C(1,5)], 29.22 [C(9)], 50.42, 53.92 [bs, C(2,4,6,8)], 61.14 (*C*-H isopropyl), 119.60, 129.36, 130.65, 141.78 (Ar-*C*), 170.05 [NH*C*(O)CH_3], 175.02 (N*C*=O); Anal. Calcd for $C_{19}H_{28}ClN_3O_6$: C, 53.08; H, 6.56. Anal. Calcd for $C_{19}H_{28}ClN_3O_6 \cdot 0.8\ H_2O$: C, 51.36; H, 6.71. Found: C, 51.27; H, 6.63.

3-(4-Fluorobenzoyl)-7-isopropyl-3,7-diazabicyclo-[3.3.1]nonane Hydroperchlorate (53b). A 250-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C) solution of amide **52d** (1.0 g, 3.44 mmol) in ether (25 mL) was added, dropwise, $HClO_4$ (60%, 0.72 g, 4.30 mmol) over a period of 5 min. This precipitate was filtered and washed with cold ether. Recrystallization (H_3COH, 15 mL) of the precipitate was followed by filtration and drying (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 1.03 g (76.3%) of salt **53b** as white platelettes; mp 246-247°C. IR (KBr) 3120 (N-H), 3010 (Ar-H), 2940, 2880 (C-H), 1625 (NC=O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.38 (d, J = 6.5 Hz, 6 H, C*H*$_3$ isopropyl), 1.81 [bd, 1 H, H(5)], 2.29 [bd, 3 H, H(5,9)], 3.34 (m, 5 H, ring protons, C-*H* isopropyl), 3.52 (bd, 4 H, ring protons), 7.17 (t, 2 H, Ar-*H*), 7.38 (m, 2 H, Ar-*H*): ^{13}C NMR (D_3CCN) ppm 16.72 (*C*H$_3$ isopropyl), 27.89 [C(1,5)], 28.99 [C(9)], 50.34, 53.52 [bs, C(2,4,6,8)], 60.96 (*C*-H isopropyl), 116.29, 116.59, 118.01, 118.36, 130.65, 130.77, 132.78, 132.82 (Ar-*C*), 162.59, 165.88 (J = 247.6 Hz,

Ar*C*-F), 174.13 (N*C*=O); Mass spectral (EI) data calcd for $C_{17}H_{24}ClN_2O_5F$ *m/z* (M+): 290.1855 (-$HClO_4$). Found: 290.1853. Anal. Calcd for $C_{17}H_{24}ClN_2O_5F$: C, 52.24; H, 6.19. Found: C, 52.46; H, 6.24.

3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Dihydroperchlorate (53c). A 250-mL Erlenmeyer flask equipped with an ice bath was added amide **52e** (1.44 g, 4.25 mmol) in 40 mL of ether/H_3COH (50:50) and was chilled to 5°C. To this new solution was added perchloric acid (60%, 1.56 g, 9.56 mmol), and immediately a white precipitate formed. The heterogeneous mixture was allowed to stir an additional 15 min at this temperature. After filtering (suction), the solid was recrystallized with hot H_3COH (35 mL) and the solution was allowed to stand at room temperature. The solid formed was filtered (suction) and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give white needles (1.14 g, 60.9%) of **53c**; mp 262-263°C. IR(KBr) 3200 (N-*H*), 3005 (Ar-C), 2940, 2880 (C-H), 1645 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 5.8 Hz, 6 H, CH_3 isopropyl), 1.71-1.92 [bd, 2 H, H(9)], 2.34-2.41 [bs, 2 H, H(1,5)], 3.23 [m, 5 H, $H(2,4,6,8)_{ax}$, C-*H* isopropyl], 3.23-3-97 [m, 4 H, $H(2,4,6,8)_{eq}$],3.94 (bs, 1 H, N-*H*), 7.66 (d, 2 H, Ar-*H*), 7.94 (s, 1 H, C-*H* imidazole), 7.96 (d, 2 H, Ar-*H*), 8.32 (s, 1 H, C-*H* imidazole), 9.20 (s, 1 H, C-*H* imidazole); ^{13}C NMR (DMSO-d_6) ppm 26.42 [C(1,5)], 27.36 [C(9)], 59.64 [C(2,4,6,8), *C*-H isopropyl], 120.63, 121.35, 122.01, 128.74, 135.27, 137.49 (Ar-*C*), 171.49 (N*C*=O); Mass spectral (EI) data calcd for $C_{20}H_{28}Cl_2N_4O_9$ m/z (M^+): 338.2106 (-2 $HClO_4$). Found: 338.2099. Anal. calcd for $C_{20}H_{28}Cl_2N_4O_9$: C, 44.54; H, 5.23; N, 10.38. Found: C, 44.75; H, 5.20; N, 10.20.

3-[4-(Nitro)phenylacetyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (53d). A solution of amide **52f** (0.55 g, 1.66 mmol) in ether (40 ml) contained in a 125-mL Erlenmeyer flask equipped with a ice bath and a magnetic stirrer was chilled

(5°C) with stirring. Upon dropwise addition of $HClO_4$ (60%, 0.35 g, 2.07 mmol), a white precipitate resulted, and the mixture was allowed to stir for 15 min at this temperature. After filtering (suction), the solid was recrystallized with a minimum amount of hot H_3COH (20 mL) and filtered hot through a flutted filter paper. Upon standing at room temperature, the solution deposited a new solid which was filtered (suction) and dried (Abderhalden, 80°C/7 mm Hg) to give 0.52 g (72.6%) of salt **53d**; mp 225-226°C. IR (KBr) 3160 (N-H), 3090 (Ar-H), 2980, 2940, 2890 (C-H), 1665 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.31 (d, J = 6.1 Hz, 6 H, C*H*$_3$ isopropyl), 1.82 [bd, 1 H, $H(9)_{ax}$], 1.95 [d, 1 H, $H(9)_{eq}$], 2.36 [s, 2 H, H(1,5)], 3.22 (m, 4 H, ring protons), 3.49 (m, 3 H, ring protons, C-*H* isopropyl), 3.94 (bs, 2 H, Ar-C*H*$_2$), 4.18 (bd, 2 H, ring protons), 7.47 (d, 2 H, Ar-*H*), 8.28 (d, 2 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 16.79 (*C*H_3 isopropyl), 27.79 [C(1,5)], 28.53 [C(9)], 41.09 (Ar-*C*H_2), 48.32, 53.81 [bs, C(2,4,6,8)], 60.95 (*C*-H iso-propyl), 118.33, 124.17, 132.02, 144.58 (Ar-*C*), 173.96 (N*C*=O); Anal. Calcd for $C_{18}H_{26}ClN_3O_7$: C, 50.06; H, 6.07. Found: C, 49.76; H, 6.16.

3-[4-(*N*-Acetyl)phenylacetyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (53e). A chilled (5°C, via ice bath) solution of amide **52h** (2.03 g, 5.91 mmol) in H_3COH/ether (50:50, 25 mL) was placed in a 125-mL Erlenmeyer flask equipped with a magnetic stirrer. Dropwise addition of $HClO_4$ (60%, 0.72 g, 4.30 mmol) over a period of 5 min was followed by continual stirring at this temperature for an additional 15 min. This precipitate was filtered and washed with cold ether. Recrystallization (H_3COH, 35 mL) of the precipitate gave a new solid which was filtered and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 1.98 g (75.4%) of salt **53e** as white platelettes; mp 197-198°C. IR (KBr) 3600 (O-H), 3360 (N-H) , 3100 (N-H), 3040 (Ar-H), 2940, 2860 (C-H), 1675 [NHC(O)CH_3], 1645 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.24 (d, J = 5.9 Hz, 6 H, C*H*$_3$ isopropyl), 1.78 [bd, 1 H, $H(9)_{ax}$], 1.91

[m, 1 H, $H(9)_{eq}$], 2.06 [s, 3 H, $NC(O)CH_3$], 2.29 [bs, 3 H, H(1,5), ring proton], 3.02-3.26 (m, 3 H, ring proton, C-*H* isopropyl), 3.43 (m, 3 H, ring proton), 3.72 (s, 2 H, Ar-CH_2), 4.19 (bd, 2 H, ring protons), 7.18 (d, 2 H, Ar-*H*), 7.51 (d, 2 H, Ar-*H*), 8.36 (bs, 1 H, $CH_3C(O)N$-*H*); ^{13}C NMR (D_3CCN) ppm 16.75 (CH_3 isopropyl), 24.29 [$NC(O)CH_3$], 27.81 [C(1,5)], 28.60 [C(9)], 41.11 (Ar-CH_2), 48.31, 53.95 [bs, C(2,4,6,8)], 60.86 (*C*-H isopropyl), 120.54, 130.72, 131.16, 138.77 (Ar-*C*), 169.56 [$NHC(O)CH_3$], 175.01 (N*C*=O); Anal. Calcd for $C_{20}H_{30}ClN_3O_6$: C, 54.11; H, 6.81. Anal. Calcd for $C_{20}H_{30}ClN_3O_6 \cdot 0.8\ H_2O$: C, 52.41; H, 6.95. Found: C, 52.52; H, 6.92.

3-[4-(Methylsulfonyl)amino]phenylacetyl-7-isopropyl-3,7-diazabicyclo[3.3.1]-nonane Hydroperchlorate (53f). To a 125-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was added sulfonamide **52i** (1.73 g, 4.56 mmol) dissolved in H_3COH/ether 1:1, 40 mL), and the resulting solution was chilled (5°C). With stirring, $HClO_4$ (60%, 0.95 g, 5.70 mmol) was added dropwise over a period of 15 min, and stirring was continued an additional 10 min at this temperature. The white precipitate was suction filtered and recrystallized from hot H_3COH (25 mL) to give 1.54 g (70.7%) of **53f** as white platelettes; mp 177.5-178.5°C. IR (KBr) 3590 (O-H), 3250 (N-H) , 3160 (N-H), 3020 (Ar-H), 2940, 2920, 2860 (C-H), 1665 (NC=O), 1100 (Cl-O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.28 (d, J = 6.4 Hz, 6 H, CH_3 isopropyl), 1.79 [bd, 1 H, $H(9)_{ax}$], 1.92 [m, 1 H, $H(9)_{eq}$], 2.33 [bs, 2 H, H(1,5)], 2.96 (s, 3 H, SO_2CH_3), 3.11-3.28 (m, 4 H, ring protons), 3.44 (m, 3 H, ring protons, C-*H* isopropyl), 3.78 (bs, 2 H, Ar-CH_2), 4.19 (bd, 2 H, ring protons), 6.58 (bs, 1 H, N-*H*), 7.23 (m, 4 H, Ar-*H*), 7.60 (s, 1 H, SO_2N-*H*); ^{13}C NMR (D_3CCN) ppm 16.67 (bs, CH_3 isopropyl), 27.79 [C(1,5)], 28.55 [C(9)], 39.56 (SO_2CH_3), 40.86 (Ar-CH_2), 48.30, 53.80 [bs, C(2,4,6,8)], 60.88 (*C*-H isopropyl), 121.93, 131.56, 132.88, 137.38 (Ar-*C*), 174.94 (N*C*=O); Anal. Calcd for $C_{19}H_{30}ClN_3O_7S$: C,

47.55; H, 6.30. Anal. Calcd for $C_{19}H_{30}ClN_3O_7S \cdot 0.4\ H_2O$: C, 46.84; H, 6.37. Found: C, 46.55; H, 6.26.

3-(4-Aminobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Dihydrochloride (54a). A 250-mL Erlenmeyer flask equipped with an ice bath and a magnetic stirrer was charged with amide **44** (2.0 g, 6.96 mmol) in ether and chilled to 5°C via ice bath. HCl gas (generated as described for **54b**) was bubbled (4 bubbles/sec) into the system over a period of 10 minutes. The resulting white precipitate was filtered with suction and washed with cold ether (10 mL). Recrystallization (H_3COH/ether, 50:50, 20 mL) was followed by filtering (suction) and drying (Abderhalden, 80°C/0.2 mm Hg, 12 h) to afford salt **54a** (1.58 g, 70.2 %); mp 209-210°C. IR (KBr) 3560 (O-H), 3400 (N-H), 3160 (NH_2), 3010 (Ar-H), 2860 (C-H), 1630 (NC=O) cm^{-1}; ^1H NMR (D_2O) δ 1.45 (d, J = 6.0 Hz, 6 H, CH_3 isopropyl), 2.03 [bs, 2 H, H(9)], 2.49 [bs, 2 H, H(1,5)], 3.40-3.67 (m, 9 H, ring protons, C-*H* isopropyl), 4.63 (s, 2 H, N-*H*), 7.62 (m, 4 H, Ar-*H*); ^{13}C NMR (D_2O) ppm 18.83 (bs, CH_3 isopropyl), 29.84 [C(1,5)], 30.14 [C(9)], 52.19, 55.26 [bs, C(2,4,6,8)], 63.65 (*C*-H isopropyl), 124.20, 131.59, 135.29, 139.39 (Ar-*C*), 177.42 (N*C*=O); Mass spectral (EI) calcd for $C_{17}H_{27}Cl_2N_3O$ *m/z* (M+): 287.1998 (-2 HCl). Found: 287.2013. Anal. Calcd for $C_{17}H_{27}Cl_2N_3O$: C, 63.05; H, 8.09. Anal. Calcd for $C_{17}H_{27}Cl_2N_3O \cdot 0.9\ H_2O$: C, 54.23; H, 7.71. Found: C, 54.56; H, 7.62.

3-(4-Nitrobenzoyl)-7-isopropyl-3,7-diazabicyclo-[3.3.1]nonane Hydrochloride (54b). Gaseous HCl was generated in a standard setup with a 250-mL collection flask containing solid NaCl. The H_2SO_4 (~15 mL) was added dropwise (1 ml/min), and the gas generated was passed through a $CaCl_2$ drying tube. Into a 250-mL Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled $HCl_{(g)}$ to a chilled (5°C) solution of amide **52a** (2.5 g, 7.88 mmol) in ether (75 mL) over a 15 min period. The

mixture was allowed to stir an additional 15 min at 0-5°C. A white precipitate was filtered and washed with cold ether (30 mL). The solid was recrystallized (H_3COH/ether, 1:1, 60 mL), and the white needles collected were washed with cold ether (25 mL) and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 2.09 g (74.9%) of salt **54b**; mp 258-259°C. IR (KBr) 3400 (N-H), 3100, 3040 (Ar-H), 2980, 2940, 2860 (C-H), 1660 (NC=O) cm^{-1}; ^1H NMR (D_2O) δ 1.44 (d, J = 6.1 Hz, 6 H, C*H*$_3$ isopropyl), 2.03 [bs, 2 H, H(9)], 2.52 [bs, 2 H, H(1,5)], 3.39-3.67 (bm, 9 H, ring protons, C-*H* isopropyl), 4.45 (s, 1 H, N-*H*), 7.71 (d, 2 H, Ar-*H*), 8.36 (d, 2 H, Ar-*H*); ^{13}C NMR (D_2O) ppm 19.82 (bs, *C*H$_3$ isopropyl), 29.36 [bs, C(1,5,9)], 49.42, 54.01 [bs, C(2,4,6,8)], 63.38 (*C*-H isopropyl), 126.89, 130.73, 143.84, 151.10 (Ar-*C*), 175.77 (N*C*=O); Mass spectral (EI) data calcd for $C_{17}H_{24}N_3O_3Cl$ *m/z* (M^+): 317.1739 (-HCl). Found: 317.1734. Anal. Calcd for $C_{17}H_{24}N_3O_3Cl$: C, 57.70; H, 6.84; N, 11.88. Found: C, 57.86; H, 6.72; N, 11.65.

3-[4-(Methylsulfonyl)amino]benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydrochloride (54c). A 250-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. Into a chilled (5°C) solution of sulfonamide **52c** (3.18 g, 8.70 mmol) in H_3COH (75 mL) was bubbled (4 bubbles/sec) HCl gas over a period of 15 min, and the resulting white precipitate was stirred for an additional 15 min at this temperature. Filtration was followed by recrystallization using H_3COH (10 mL) which was warmed on a hot plate. To the slightly heated solution was added ether (~35 mL) to reach the cloud point, and the resulting solution was allowed to cool to room temperature. The precipitate was filtered (suction) and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 1.13 g (33.8 %) of **54c**; mp 203-204°C. IR (KBr) 3575 (O-H), 3420 (N-H) , 3240 (N-H), 3080, 3020 (Ar-H), 2960, 2880, 2800 (C-H), 1720 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 (d, J = 6.5 Hz, 6 H, C*H*$_3$ isopropyl), 1.82 [m, 2 H, H(9)], 2.36 [bs, 2 H, H(1,5)], 3.11 (s, 3 H, SO_2CH_3), 3.29 (m, 5 H, ring protons, C-*H* isopropyl), 3.35 (d, J = 13.1 Hz, 2 H,

ring protons), 3.60 (d, J = 13.1 Hz, 2 H, ring protons), 7.32 (d, 2 H, Ar-*H*), 7.94 (d, 2 H, Ar-*H*), 9.72 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.92 (CH_3 isopropyl), 25.21 [C(1,5 9)], 43.81 (SO_2CH_3), 50.65, 51.72 [C(2,4,6,8)], 61.09 (*C*-H isopropyl), 117.56, 123.77, 130.62, 143.01 (Ar-*C*), 165.66 (N*C*=O); Mass spectral (EI) data calcd for $C_{18}H_{28}ClN_3O_3S$ *m/z* (M+): 365.1773 (-HCl). Found: 365.1754. Anal. Calcd for $C_{18}H_{28}ClN_3O_3S$: C, 53.79; H, 7.02. Anal. Calcd for $C_{18}H_{28}ClN_3O_3S \cdot 2.5\ H_2O$: C, 48.37; H, 7.44. Found: C, 48.46; H, 7.37.

3-[(4'-Fluorobenzoyl)methyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (55a). To a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a heating mantle, a 25-mL addition funnel, and a condenser with an N_2 inlet were added 2-chloro-4'-fluoroacetophenone (**66**, 7.55 g, 43.8 mmol) and NaI (9.85 g, 65.7 mmol) in H_3CCN (30 mL), the mixture was heated for 30 minutes with stirrring. The new solution was allowed to cool to room temperature (30 min) which was followed by dropwise addition of amine **52j** (6.7 g, 39.8 mmol) to give a light yellow mixture which was stirred overnight. Filtration (suction) removed excess NaI, and the filtrate was diluted with H_2O and transferred to a separatory funnel. The resulting homogenous solution (pH~5) was extracted (ether, 3 x 75 mL) with the latter being discarded, and the pH of the aqueous layer was adjusted to 12 using 10% NaOH. Extraction (ether, 3 x 75 mL) of the aqueous layer was followed by another extraction (H_2CCl_2, 3 x 75 mL) and the ether extracts were discarded. The organic layer (H_2CCl_2) was dried (Na_2SO_4, 2 h), filtered, and concentrated (rotary evaporator) to give 2.9 g (86.1 %) of amine **55a** as a light yellow solid; mp 193-194°C. IR (KBr) 3060, 3040 (Ar-H), 2940, 2805 (C-H), 1700 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.45 (d, J = 6.3 Hz, 6 H, CH_3 isopropyl), 1.81 [d, J = 10.1 Hz, 1 H, $H(9)_{ax}$], 2.11 [d, J = 10.1 Hz, 1 H, $H(9)_{eq}$], 2.32 [bs, 2 H, H(1,5)], 2.85 (d, J = 11.4 Hz, 2 H, ring protons), 3.37 (d, J = 13.2 Hz, 2 H, ring protons), 3.49 (d, J = 11.4 Hz, 2 H, ring

protons), 3.86 (m, 3 H, ring protons, C-*H* isopropyl), 4.18 (s, 2 H, ArC(O)C*H*$_2$), 7.15 (t, 2 H, Ar-*H*), 8.02 (m, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 17.01 (*C*H$_3$ isopropyl), 28.04 [C(1,5)], 30.05 [C(9)], 53.74, 57.22, 57.34 [C(2,4,6,8), *C*-H isopropyl)], 62.22 [ArC(O)*C*H$_2$], 115.58, 115.88, 130.57, 130.70, 131.22, 131.26 (Ar-*C*), 164.10, 167.49 (J = 265.8 Hz, Ar*C*-F), 194.99 (*C*=O). Ketone **55a** decomposes upon standing, and thus was immediately reduced to alcohol **55b**.

(±)-3-[(4'-Fluoro)-1-hydroxy-1-phenylethyl]-7-isopropyl-3,7-diazabicyclo-[3.3.1]nonane (55b). To a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser with an N_2 inlet, and two glass stoppers was added solid $LiAlH_4$ (95%, 0,787 g, 19.7 mmol) in one portion. After purging the flask with N_2 for 10 min, dry tetrahydrofuran (10 mL: freshly distilled from Na metal) was poured slowly over the $LiAlH_4$ which resulted in a gray slurry. Ketone **55a** (2.0 g, 6.57 mmol) was added portionwise over a period of 15 min, followed by heating the reaction mixture (40°C, 3 h) and then stirring at room temperature overnight. Excess $LiAlH_4$ was cautiously destroyed using EtOAc (10 mL) added dropwise to the chilled (5°C) reaction mixture. Addition of 5% HCl (~15 mL) adjusted the pH (~2) of aqueous solution which was then extracted (ether, 2 x 30 mL) to remove small impurities, and these ether extracts were discarded. After making the aqueous phase slightly basic (pH~8) using 10% NaOH (~10 mL), extraction (H_2CCl_2, 3 x 50 mL) was followed by washing the organic layer with H_2O (75 mL), satd NaCl (75 mL), and dried (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) resulted in 1.33 g (66.2%) of racemic alcohol **55b** as a white solid; mp 53-54°C. IR (film) 3225 (OH), 2930, 2800 (C-H), 1600 (C=C) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.08 (d, J = 5.9 Hz, 6 H, C*H*$_3$ isopropyl), 1.57 [bs, 2 H, H(9)], 1.87 [bs, 2 H, H(9)], 2.26 (m, 2 H, ring protons), 2.45 (bd, 2 H, ring protons), 2.55 [dd, J = 13.1 Hz, J = 4.09 Hz, 2 H, ArCH(OH)C*H*$_2$], 2.83 (bs, 2 H, ring protons), 3.07 (m, 3 H, ring

protons, C-*H* isopropyl), 4.67 [dd, J = 4.09 Hz, 1 H, ArC*H*(OH)], 6.23 (bs, 1 H, O-*H*), 7.01 (t, 2 H, Ar-*H*), 7.35 (m, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 18.39, 18.69 (*C*H_3 isopropyl), 30.17, 30.90 [C(1,5)], 32.54 [C(9)], 54.07, 54.38, 54.61, 55.24 [C(2,4,6,8)], 59.55 (*C*-H isopropyl), 64.47 [ArCH(OH)*C*H_2], 68.54 [Ar*C*-H(OH)], 114.71, 114.99, 127.39, 127.49, 138.97, 139.00 (Ar-*C*), 160.28, 163.51 (J = 243.9 Hz, Ar*C*-F); Anal. Calcd for $C_{18}H_{27}FN_2O$: C, 70.56; H, 8.88. Found: C, 70.28; H, 9.00.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydrochloride (56). Gaseous HCl was generated in a 250-mL collection flask containing solid NaCl as described for **54b**. The H_2SO_4 (~15 mL) was added dropwise, and the gas generated was passed through a $CaCl_2$ drying tube. Into a 250-mL, Erlenmeyer flask equipped with a magnetic stirrer and an ice bath was bubbled (4 bubbles/sec) $HCl_{(g)}$ to a chilled (5°C) solution of amine **73** (5.00 g, 20.20 mmol) in ether (150 mL) over a 15 min period. The mixture was allowed to stir an additional 15 min at 0-5°C. A white precipitate formed and was filtered and washed with cold ether (30 mL). The solid was recrystallized (H_3COH/ether, 1:1, 60 mL), and the white solid collected were washed with cold ether (25 mL) and dried (Abderhalden, 80°C/0.2 mm Hg, 12 h) to give 3.31 g (60.7%) of salt **56**; mp 246.0-247.0°C. IR (KBr) 3040 (Ar-H), 2950 (C-H), 735, 700 (C-H out of plane, mono) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.84 [m, 2 H, H(9)], 2.38 [m, 2 H, H(1,5)], 2.71 [d, J = 11.9 Hz, 2 H, H(6,8)$_{ax}$], 3.13 [d, J = 11.9 Hz, 2 H, H(2,4)$_{ax}$], 3.36 [bs, 2 H, H(6,8)$_{eq}$], 3.60 [d, J = 10.3 Hz, 2 H, H(2,4)$_{eq}$], 4.29 (d, 2 H, C*H*$_2$Ph), 7.61-7.49 (Ar-*H*), 9.25 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 25.96 [C(1,5)], 28.65 [C(9)], 30.91 [C(2,4)], 56.41 [C(6,8)], 60.82 (*C*H_2Ph), 129.21, 129.82, 130.19, 130.43 (Ar-*C*); Mass spectral (EI) data calcd for $C_{14}H_{20}NSCl$ *m/z* (M+): 233.1238. Found: 233.1239. Anal. Calcd for $C_{14}H_{20}NSCl$: C, 62.32; H, 7.47; N, 5.19. Found: C, 62.20; H, 7.38; N, 5.16.

Attempted Preparation of 4-(1*H*-Imidazol-1-yl)benzoyl chloride (61). To a 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirrer, condenser with N_2 inlet was added ester **59** (4.2 g, 20.77 mmol) in H_3COH (20 mL), H_2O (40 mL) and NaOH pellets (1.67 g, 41.54 mmol). The solution was then flushed with N_2. After stirring overnight at room temperature, the new solution was chilled (5°C) and treated dropwise with conc HCl (20 mL) which resulted in formation of a white precipitate. Filtration (suction) was followed by drying (Abderhalden, 80°C/7 mm Hg, 12 h). To a 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser with a N_2 inlet containing acid **60** (3.0 g, 15.94 mmol) was added thionyl chloride (18.9 g, 159.4 mmol), and the resulting heterogeneous mixture was stirred at room temperature overnight. Excess thionyl chloride was removed by distillation (aspirator), and the oil was placed on a vacuum pump (RT/7 mm Hg, 4 h) to remove any residual thionyl chloride; 3.01 g (92.1%). IR (KBr) analysis of the oil revealed absorption at 3300, 2600 (O-H), 1755 (C=O) cm^{-1}. This IR analysis indicated the presence of the carboxylic acid (O-H) stretching, but the carbonyl absorption is not in the range of amide carbonyls (1660-1620 cm^{-1}).[71] This implies that mostly starting material **60** was recovered. The reaction was attempted again but with heating of the starting acid and thionyl chloride for 4 h. After the usual workup, only the starting carboxylic acid **60** could be isolated.

Attempted Preparation of 4-(1*H*-Imidazol-1-yl)benzoyl chloride (63). To a 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirrer, condenser with an N_2 inlet were added ester **59** (1.42 g, 7.02) in H_2O:H_3COH (2:1, 30 mL) and NaOH pellets (0.536 g, 14.04 mmol),. The resulting solution was stirred at room temperature overnight. Concentration (rotary evaporator) of the solution gave a off-white solid **62** which was dried (Abderhalden, 80°C/7 mm Hg, overnight). Into a

200-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer, a condensor with an N_2 inlet, and an ice bath was added sodium salt **62** (5.87 g, 27.92 mmol), benzene (50 mL), and pyridine (3.31 g, 41.88 mmol), and the resulting mixture was cooled (5°C, via ice bath). Dropwise addition of oxalyl chloride (35.28 g, 277.93 mmol) over a period of 15 min was followed by continual stirring at this temperature and then at room temperaure overnight. Concentration (rotary evaporator) resulted in formatiom of 5.5 g (94.8%) of an off-white solid; IR (KBr) 3300, 2600 (O-H), 1755 (C=O) cm^{-1}. IR analysis indicated the presence of the carboxylic acid (O-H) stretching, but the carbonyl (C=O) absorption is not in the range of amide carbonyls (1660-1620 cm^{-1}).[71] Thus, mostly starting material **62** was recovered. The experiment was performed again using the same procedure except that after stirring the mixture in the presence of oxalyl chloride for 4 h, another portion of the oxalyl chloride (35.28 g, 277.93 mmol) was added dropwise. Stirring of the resulting mixture was continued overnight at room temperature. After the usual workup, IR analysis of the isolated product revealed that only the starting sodium salt **62** was present.

4-Nitrophenylacetyl chloride (65). To a 250-mL, round-bottomed-flask equipped with a magnetic stirrer and a condenser with a N_2 inlet. The flask was initially charged with 4-nitrophenylacetic acid (**64**, 15.0 g, 82.8 mmol) followed by addition of thionyl chloride (98.5 g, 828 mmol), and the resulting solution was allowed to stir at room temperature overnight. This light brown solution was distilled under vacuum (35°C/40 mm Hg) to remove excess thionyl chloride, and the resulting oil was then placed on a vacuum pump (RT/7 mm Hg). The acid chloride **65** was used immediately without any further purification to prepare amide **52f**.

Attempted Preparation of 3-[4'-(1*H*-Imidazol-1-yl)benzoylmethyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (67). *Method A*: A 50-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condensor with N_2 inlet and two glass stoppers. To a solution of ketone **55a** (0.100 g, 0.33 mmol) in DMSO (10 mL) was added imidazole (0.027 g, 0.396 mmol), potassium carbonate (anhydrous, 0.068 g, 0.495 mmol), and 18-crown-6 (50 mg). The stirred mixture was heated at 110°C for 8 h under N_2 via the use of boiling toluene (bp 110°C) in the jacket. Cooling the solution to RT was followed by the addition of chilled H_2O (75 mL). Combined extracts (H_2CCl_2, 4 x 40 mL) of the suspension were washed with H_2O (80 mL) and satd NaCl (80 mL); the solution was then dried (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) gave 0.091 g (78.4%) of a light yellow solid [which was placed on a vacuum pump overnight (RT/7.0mm Hg)]. IR, ^1H, and ^{13}C NMR signals of the obtained product matched those of the starting ketone **55a**. The above reaction was attempted several times using different conditions. Variations were utilized in terms of the amounts of imidazole (1.2, 1.5, 2.5, and 4.0 equivalents) and potassium carbonate (0.95, 1.1, 1.5 equivalents). The end result to all of these modified conditions was the isolation of only starting material **55a** from a mixture.

Method B: A 50-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condensor with N_2 inlet and two glass stoppers. To a solution of ketone **55a** (0.100 g, 0.33 mmol) in DMSO (10 mL) was added imidazole (0.027 g, 0.396 mmol), 2,2,6,6-tetramethylpiperidine (0.044 g, 0.314 mmol), and 18-crown-6 (50 mg). The stirred mixture was heated at 110°C for 8 h under N_2 via the use of boiling toluene (bp 110°C) in the jacket. Cooling the solution to RT was followed by the addition of chilled H_2O (75 mL). Combined extracts (H_2CCl_2, 4 x 40 mL) of the suspension were washed with H_2O (80 mL) and satd NaCl (80 mL); the solution was then dried (Na_2SO_4, 2 h). Filtration and concentration (rotary evaporator) gave 0.095 g (81.9%) of a light yellow solid [which was placed on a vacuum pump overnight

(RT/0.2mm Hg)]. IR, ^{1}H and ^{13}C NMR signals of the obtained product matched those of the starting ketone **55a**. This particular reaction was attempted because it was felt that the potassium carbonate was extracting one of the alpha protons next to the carbonyl. It was anticipated that the use of a large, hindered base such as 2,2,6,6-tetramethylpiperidine might alleviate this problem. Unfortunately, the final result was unchanged in that after workup, only starting ketone **55a** was recovered.

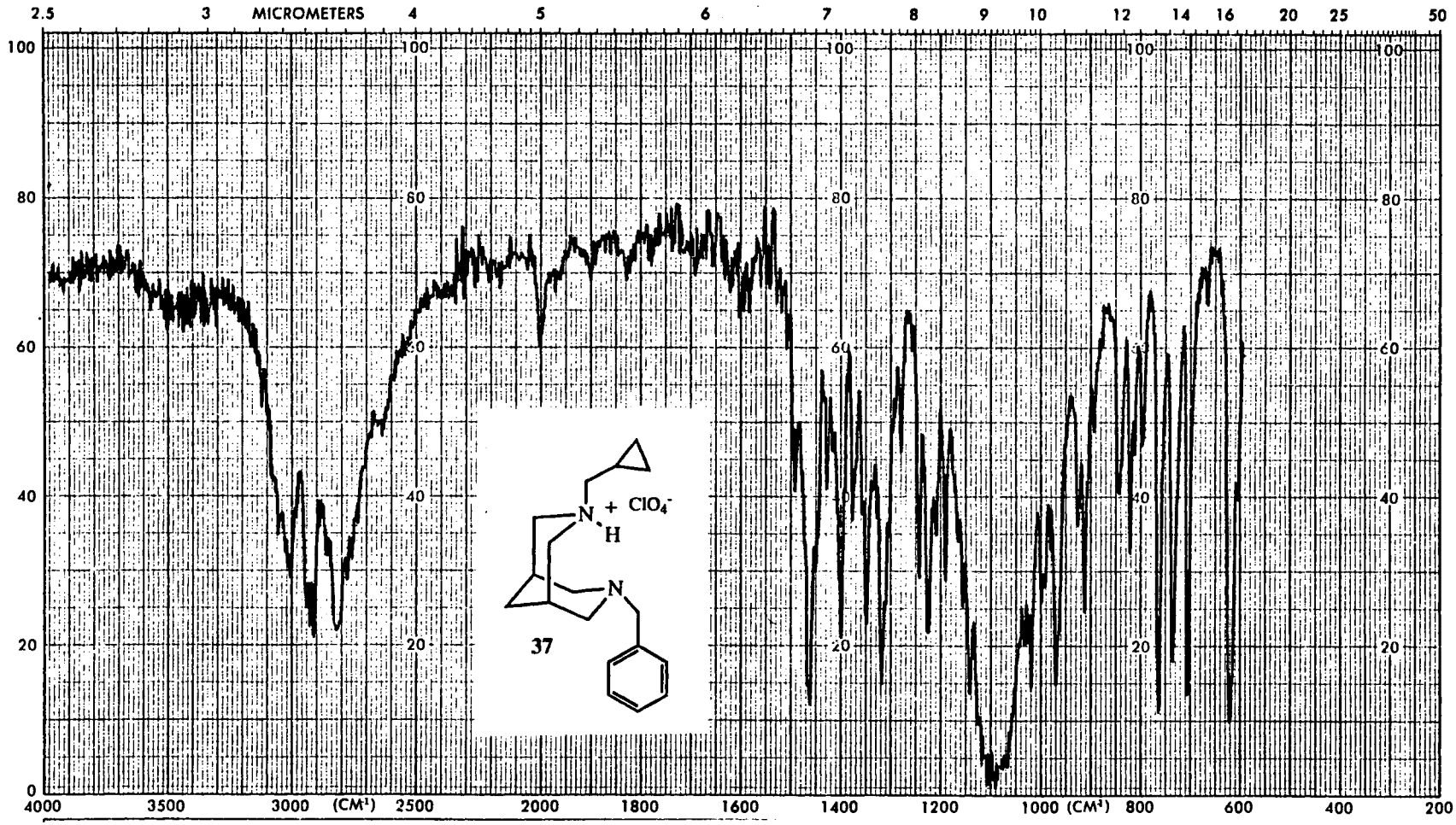
Attempted Preparation of 3-[(4'-Fluorobenzoyl)methyl]-7-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane Hydroperchlorate (68). A 100-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C) solution of amine **55a** (1.0 g, 3.29 mmol) in H_3COH/ether (50:50, 25 mL) was added dropwise $HClO_4$ (60%, 0.72 g, 0.689 mmol) over a period of 5 min. The resulting oil was isolated via decantation of the mother liquor. Crystallization of the oil was attempted using hot H_3COH (15 mL) from which, after cooling to RT, the product oiled out of solution. Trituration (ether, 15 mL) of the oil was uneffective to induce formation of a solid. IR and ^{1}H analyses of the crude oil indicated the presents of an 1,1-diol at the 1'-position on the side chain (no carbonyl). Formation of the diol presumably prevented solidification of the salt. 1,1-Diol formation at the C-9 position of certain DHBCNs via, for example, reaction of 3,7-diheterabicyclo[3.3.1]nonan-9-one and $HClO_4$ are known.[8]

Attempted Preparation of (±)-3-[(4'-Fluoro)-1-hydroxy-1-phenylethyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (69). A 100-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5°C) solution of alcohol **55b** (0.10 g, 0.328 mmol) in H_3COH/ether (50:50, 25 mL) was added dropwise $HClO_4$ (60%, 0.068 g, 0.408 mmol) over a period of 5 min. The resulting oil was isolated via decantation of the mother liquor. Crystallization of the oil

was attempted using hot H_3COH (15 mL) from which a product precipitated. Trituration (ether, 15 mL) of the oil did not induce formation of a solid. IR analysis indicated the presence of an O-H stretch (3600-3100 cm^{-1}) and the conclusion was that starting alcohol was present in large quantities. Unfortunately, it was not possible to crystallize compound **69** from this reaction mixture.

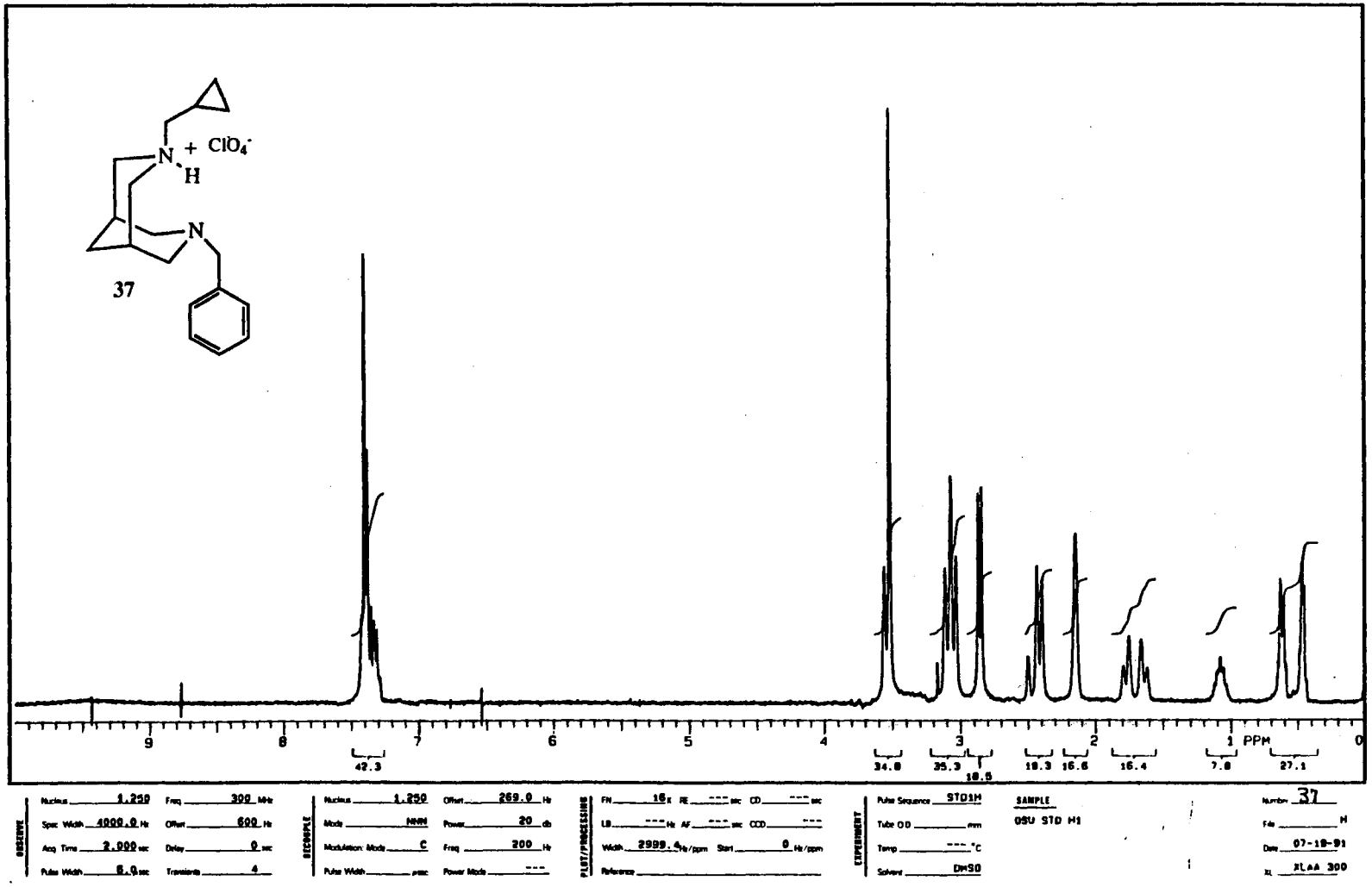
Attempted Preparation of 3-[(4'-Nitrobenzoyl)methyl]-7-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane (71). To a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a heating mantle, a 25-mL addition funnel, and a condenser with an N_2 inlet were added 2-bromo-4'-nitroacetophenone (**70**, 5.55 g, 22.7 mmol) and NaI (5.11 g, 34.1 mmol) in H_3CCN (30 mL). The resulting mixture was heated for 30 minutes with stirrring. The resulting dark brown mixture was allowed to cool to room temperature (30 min) which was followed by dropwise addition of amine **52j** (3.47 g, 20.64 mmol) to give a dark brown mixture which was stirred overnight. Filtration (suction) removed excess NaI and the filtrate was diluted with H_2O and transferred to a separatory funnel. The resulting acidic (pH~5) heterogeneous solution was adjusted to pH 12 using 10% NaOH. Extraction (ether, 3 x 75 mL) of the aqueous layer was followed by another extraction (H_2CCl_2, 3 x 75 mL) and the ether extracts were discarded. The organic layer (H_2CCl_2) was dried (Na_2SO_4, 2 h), filtered, and concentrated (rotary evaporator) to give 2.86 g (41.9 %) of dark brown oil. IR, ^1H, and ^{13}C NMR analyses of this product matched those of the starting amine **52j**.

Plate I



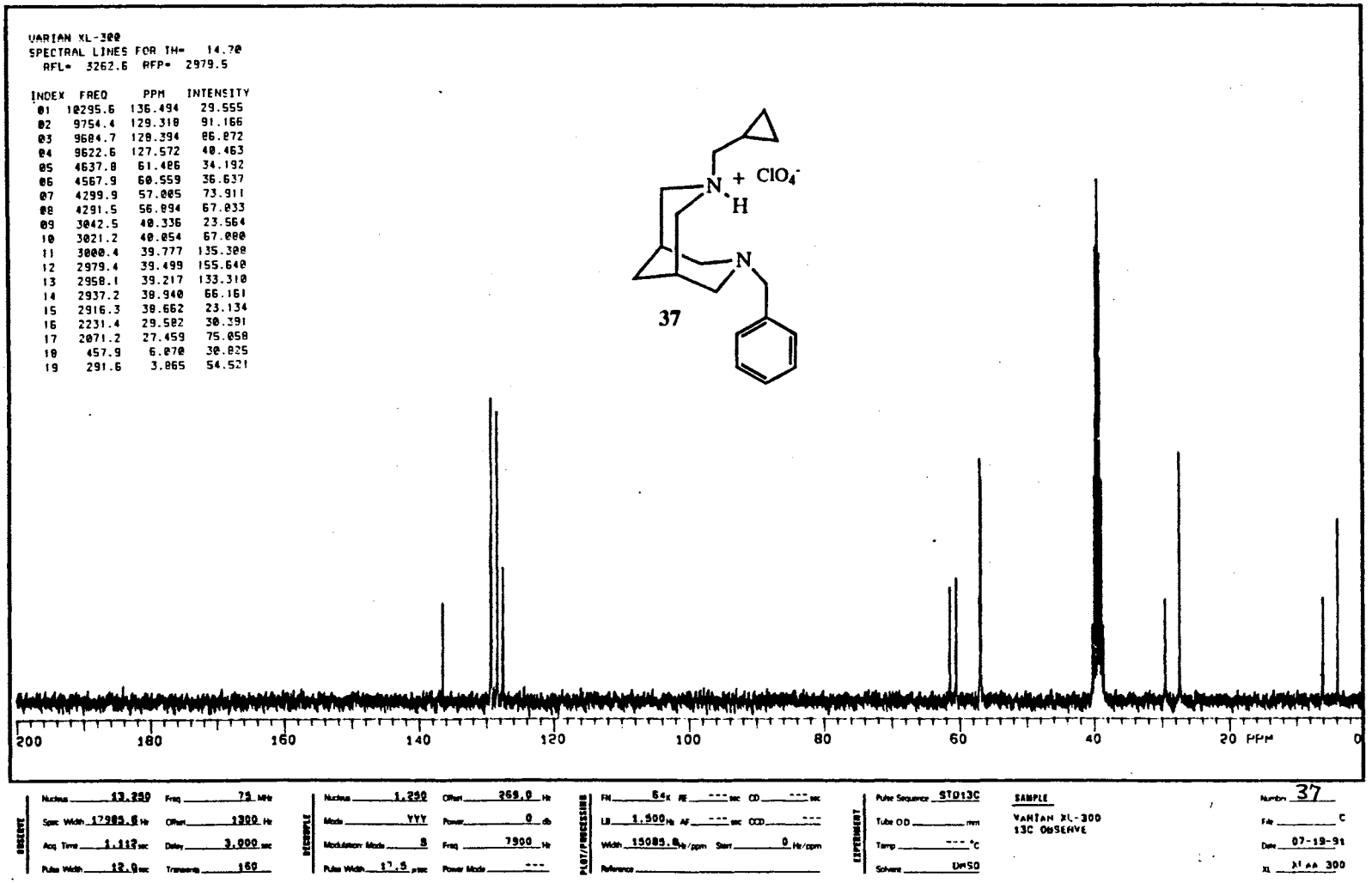
IR Spectrum of **37**

Plate II



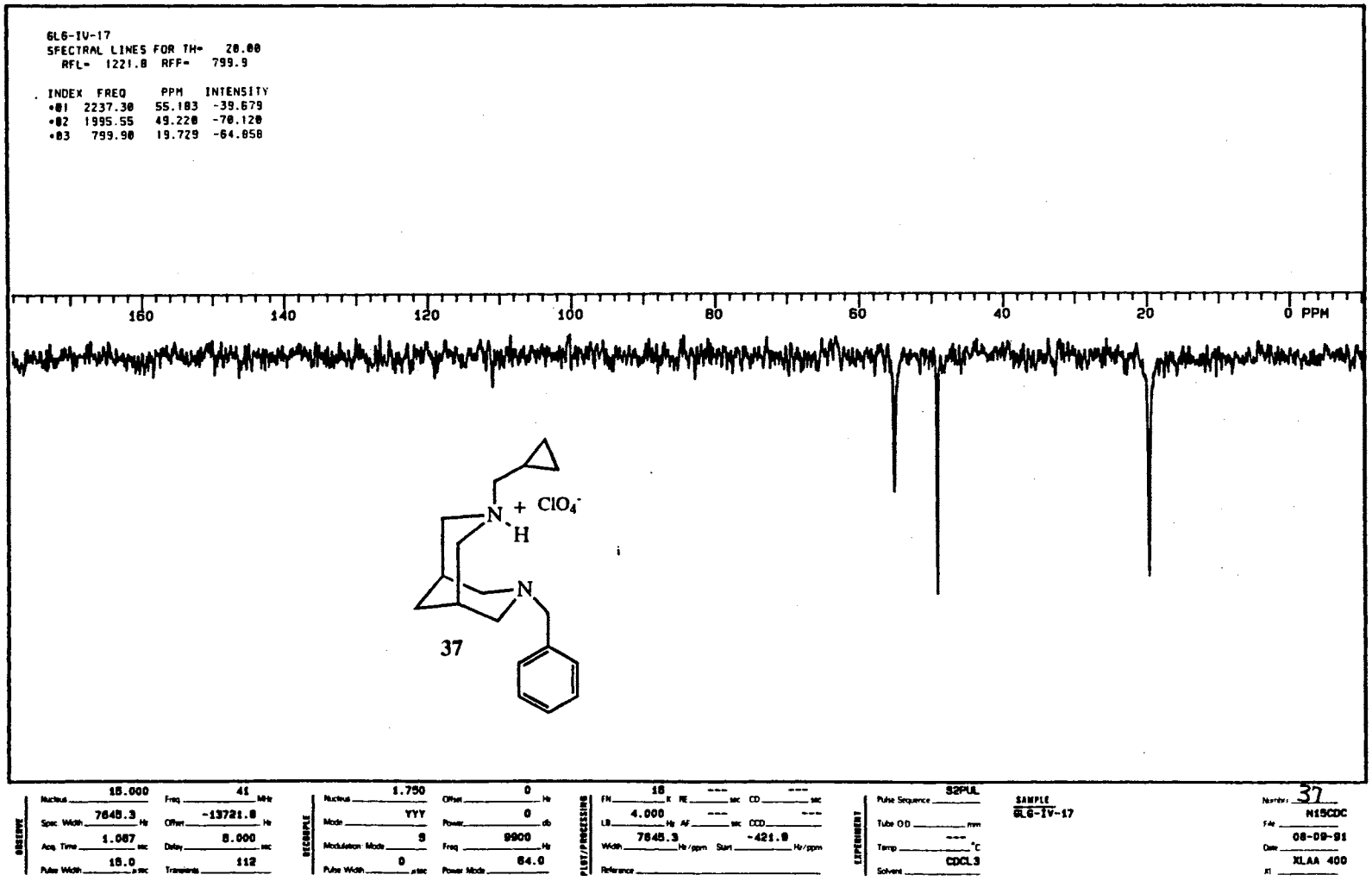
^{1}H NMR Spectrum of **37**

Plate III



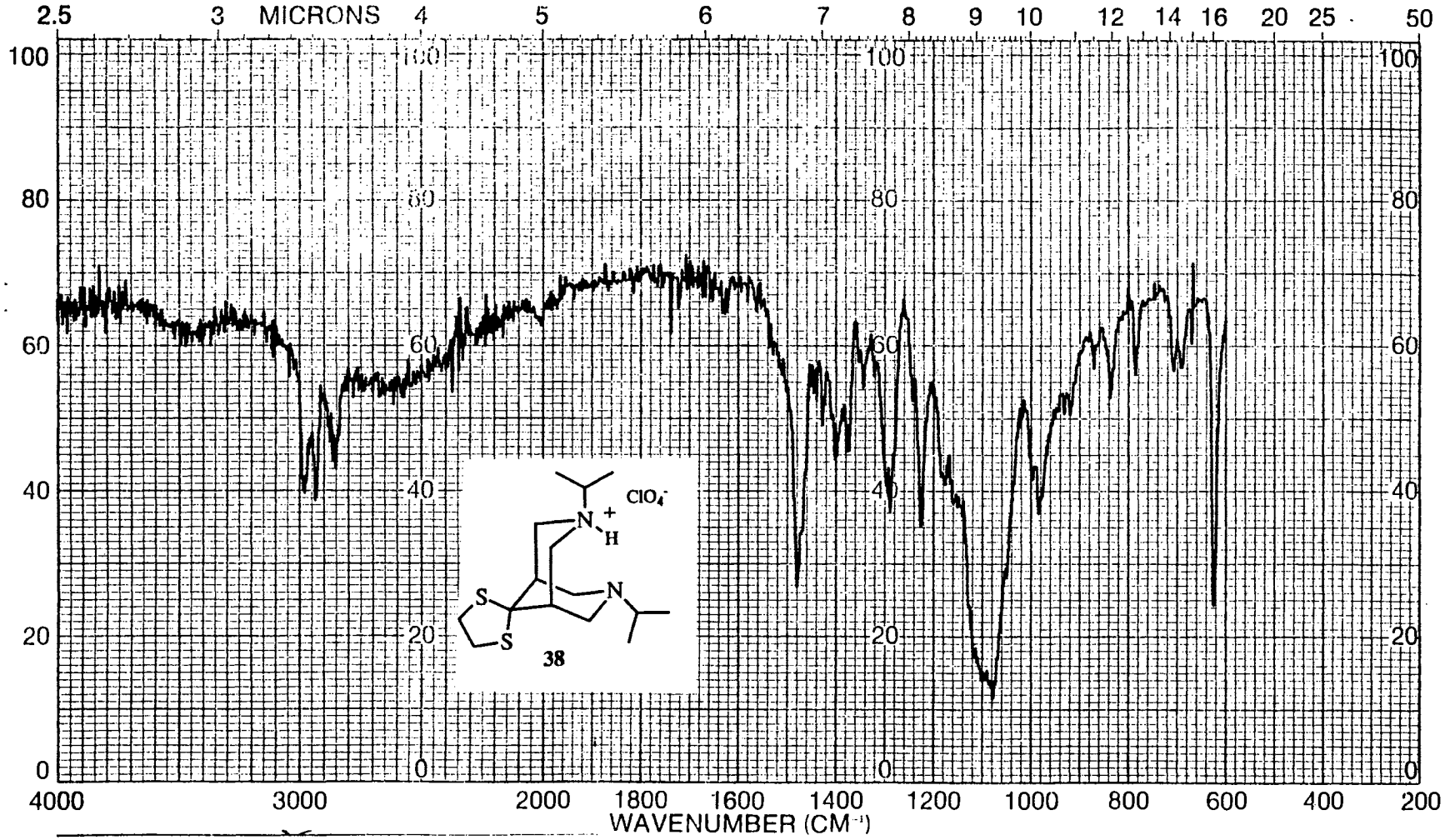
^{13}C NMR Spectrum of **37**

Plate IV



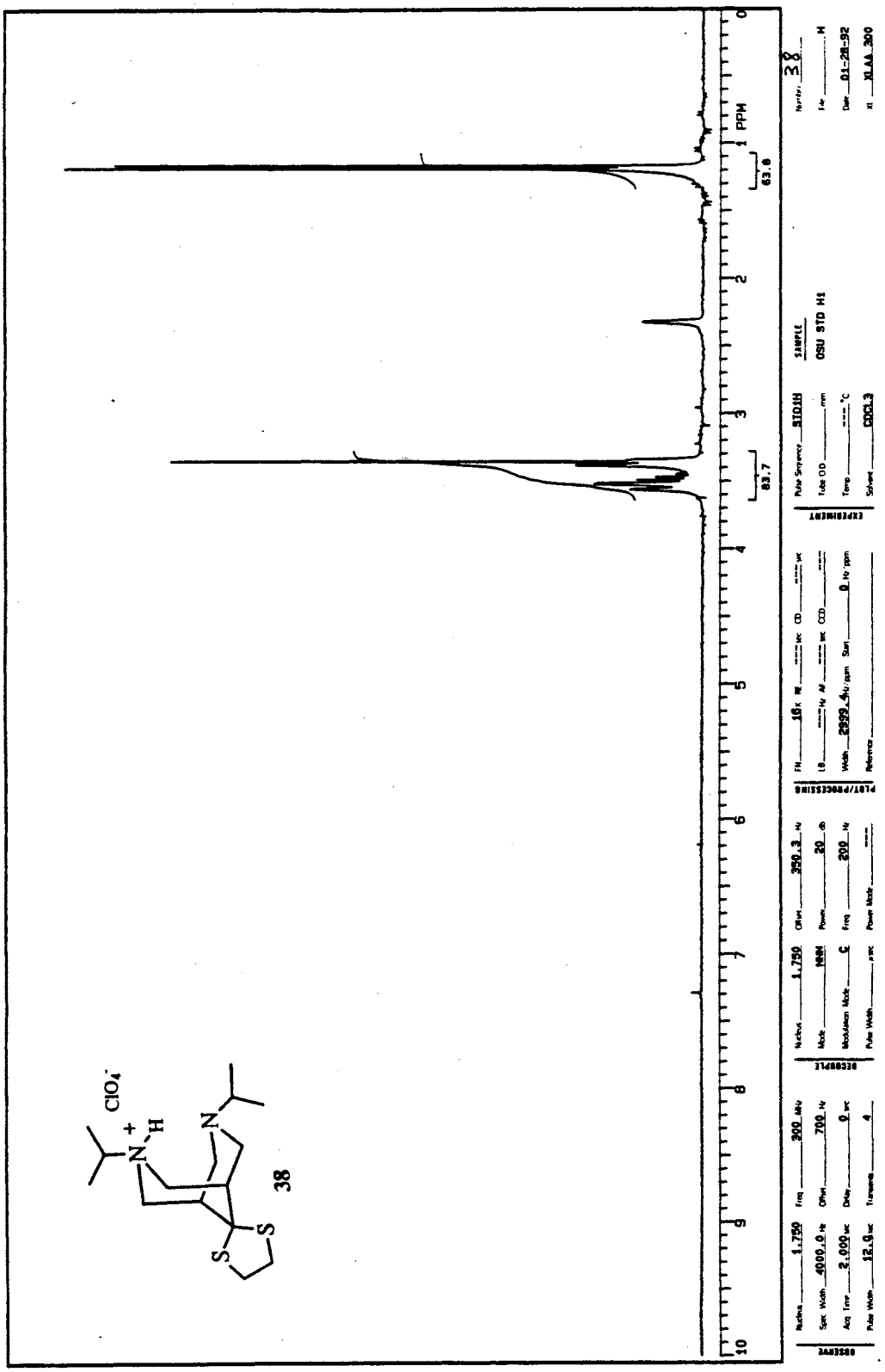
^{15}N NMR Spectrum of **37**

Plate V



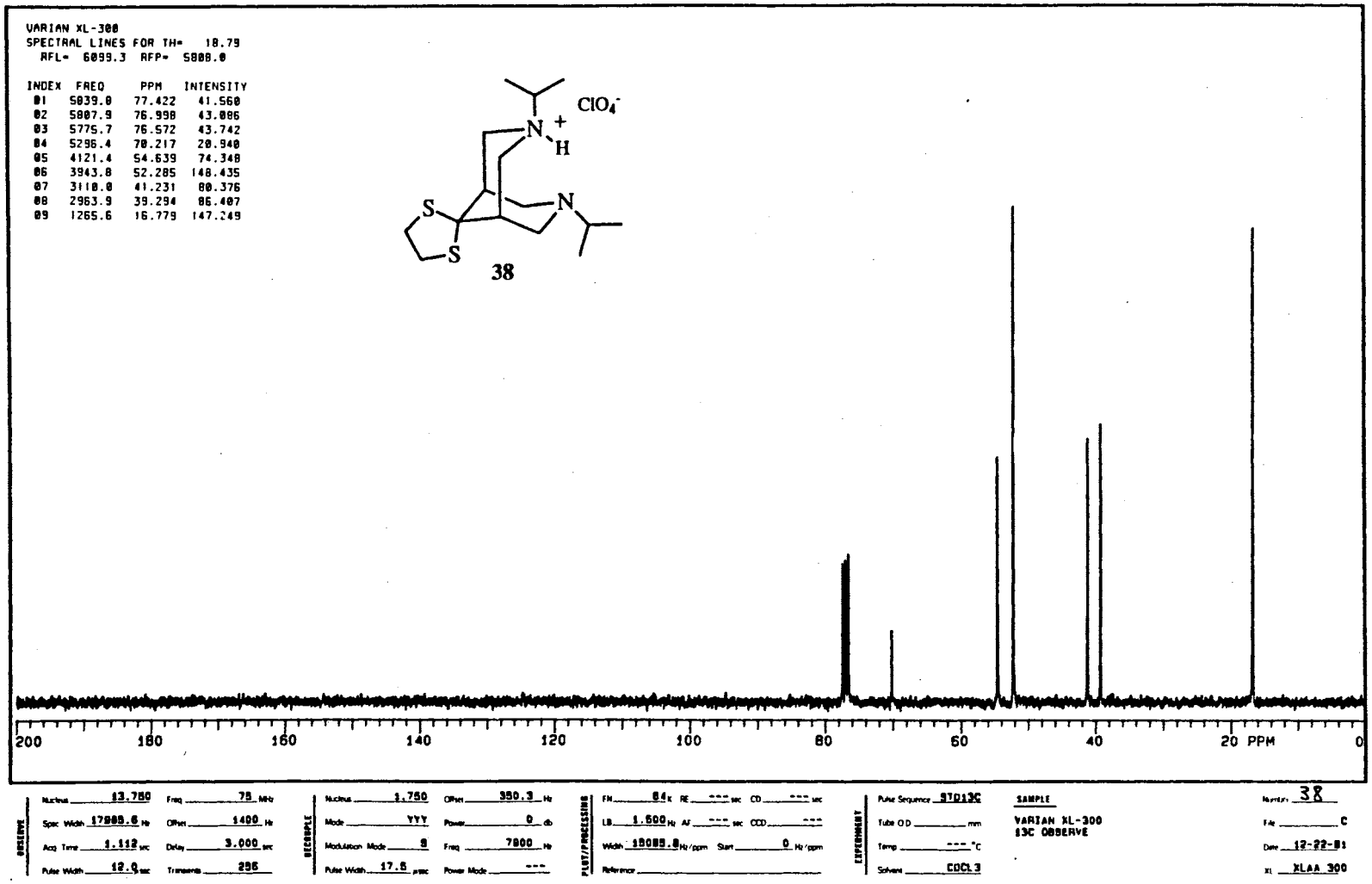
IR Spectrum of **38**

Plate VI



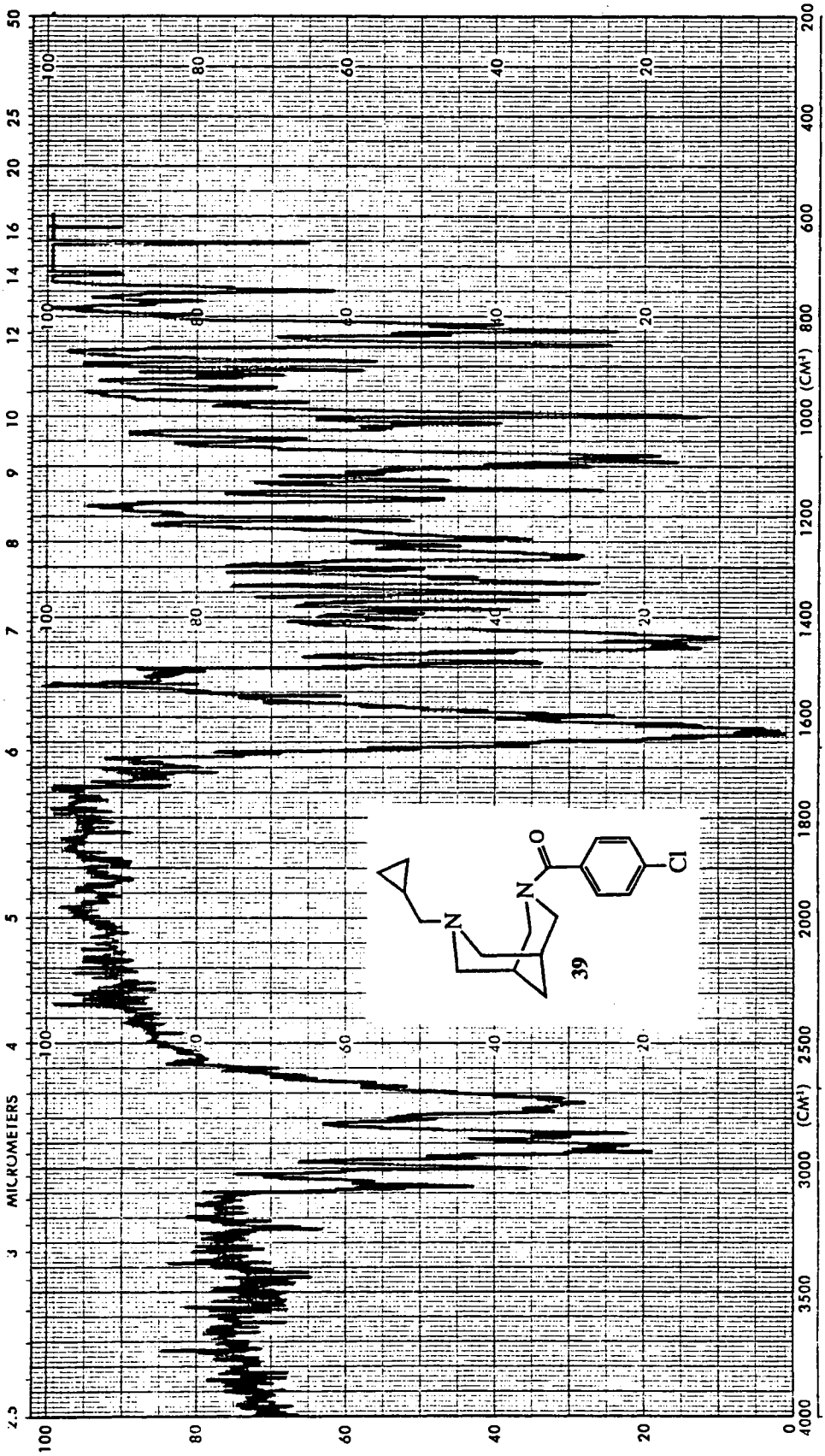
^{1}H NMR Spectrum of 38

Plate VII



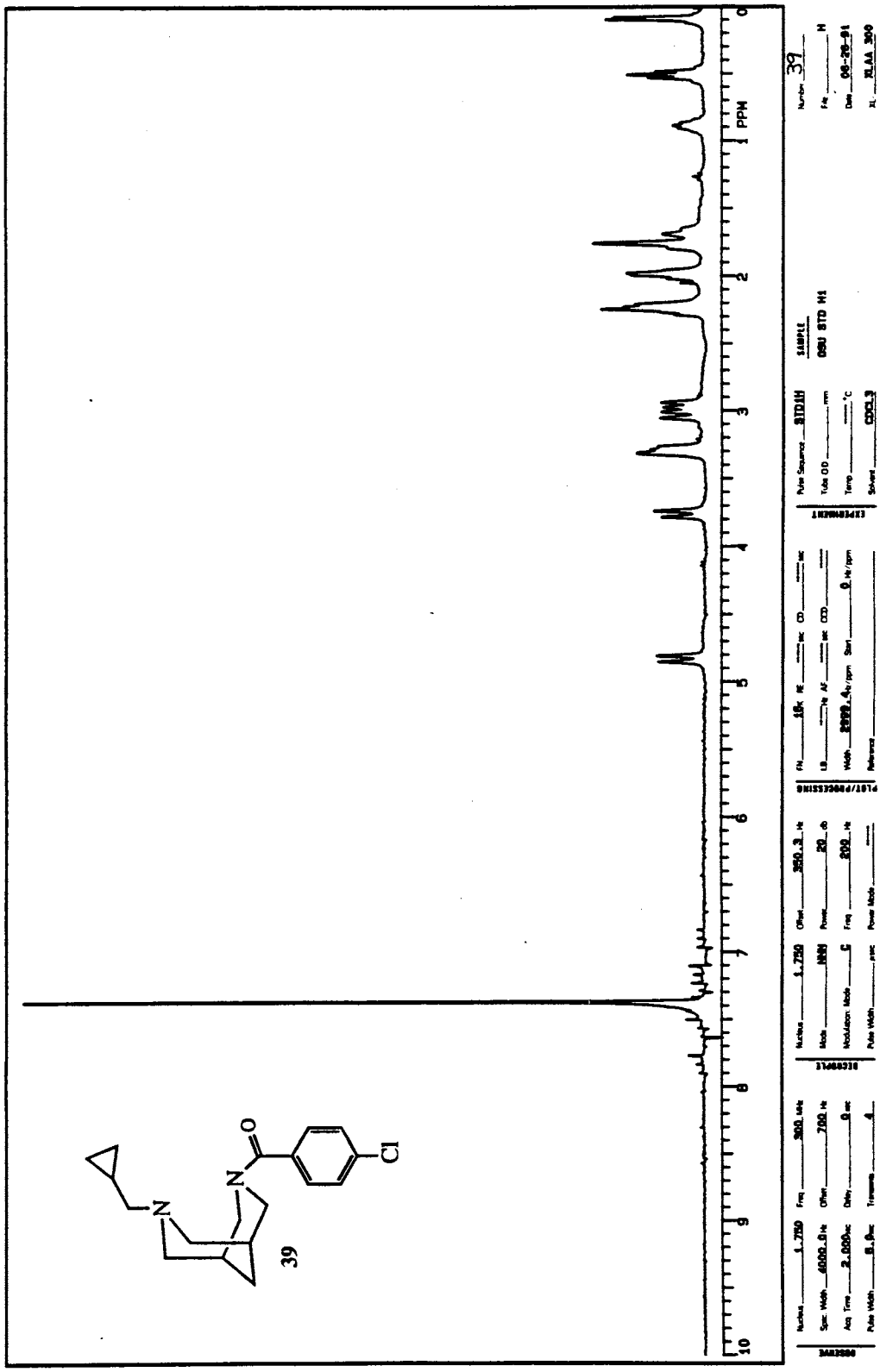
^{13}C NMR Spectrum of **38**

Plate VIII



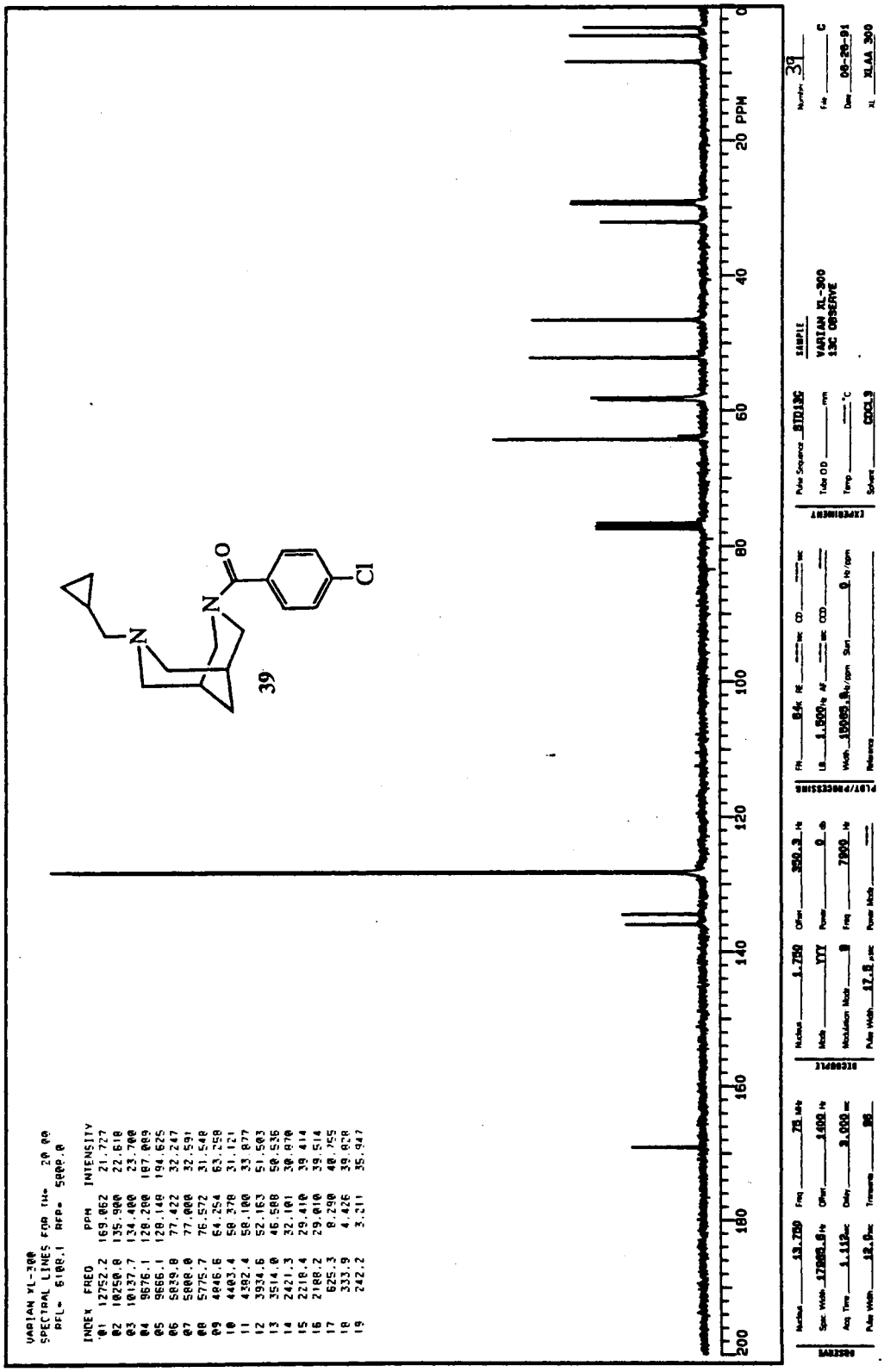
IR Spectrum of **39**

Plate IX



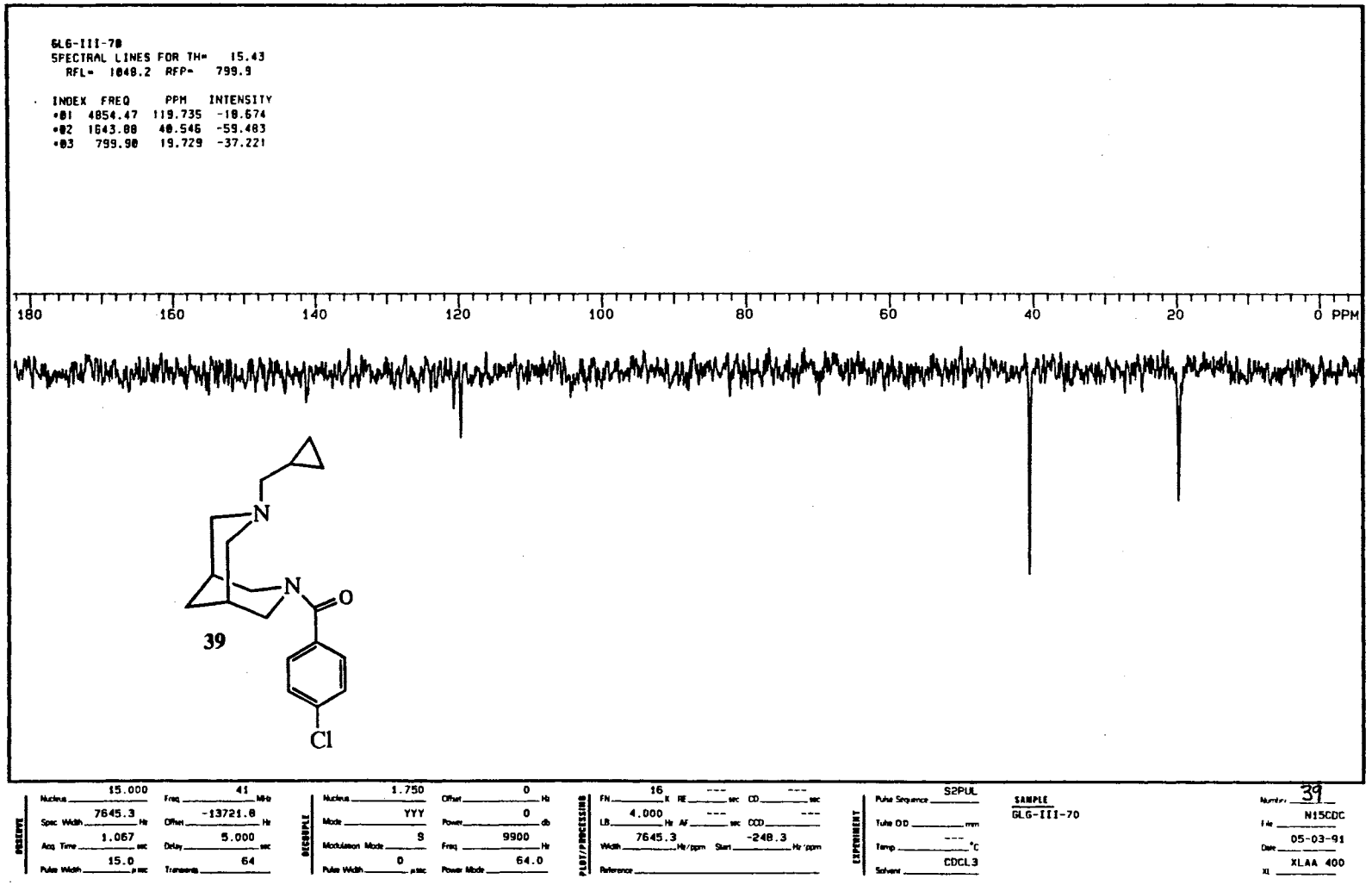
^{1}H NMR Spectrum of 39

Plate X



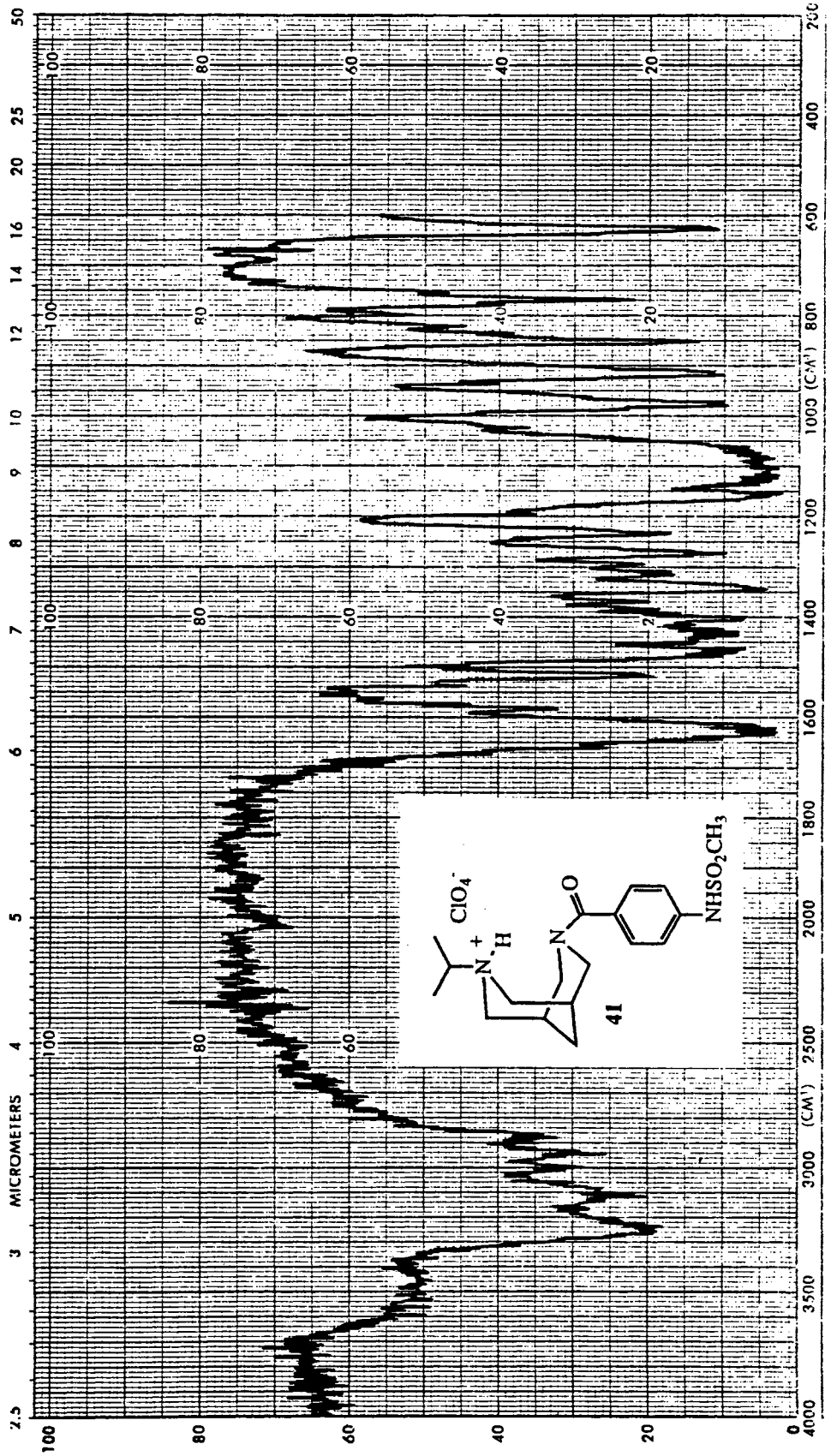
^{13}C NMR Spectrum of 39

Plate XI



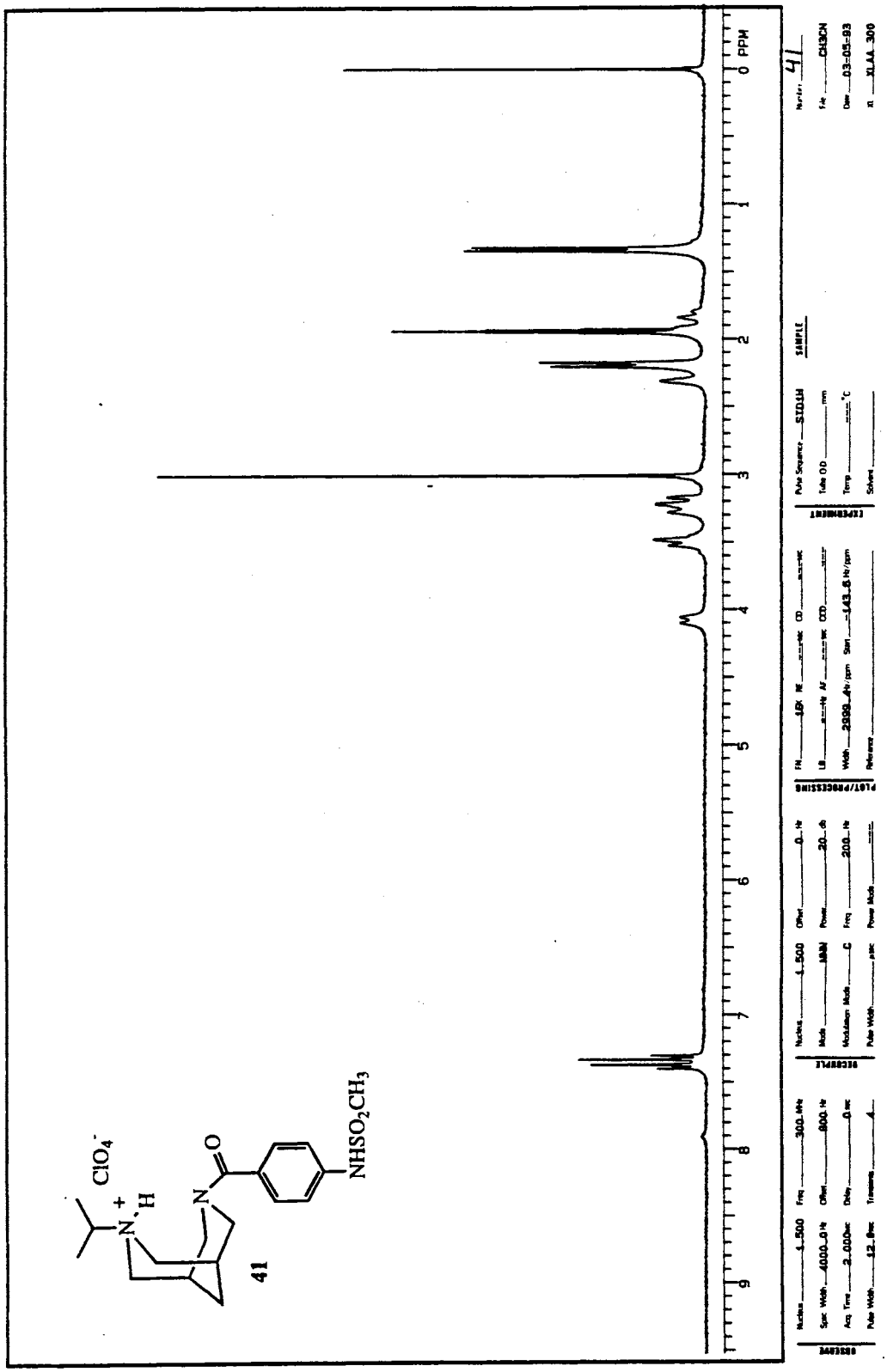
^{15}N NMR Spectrum of **39**

Plate XII



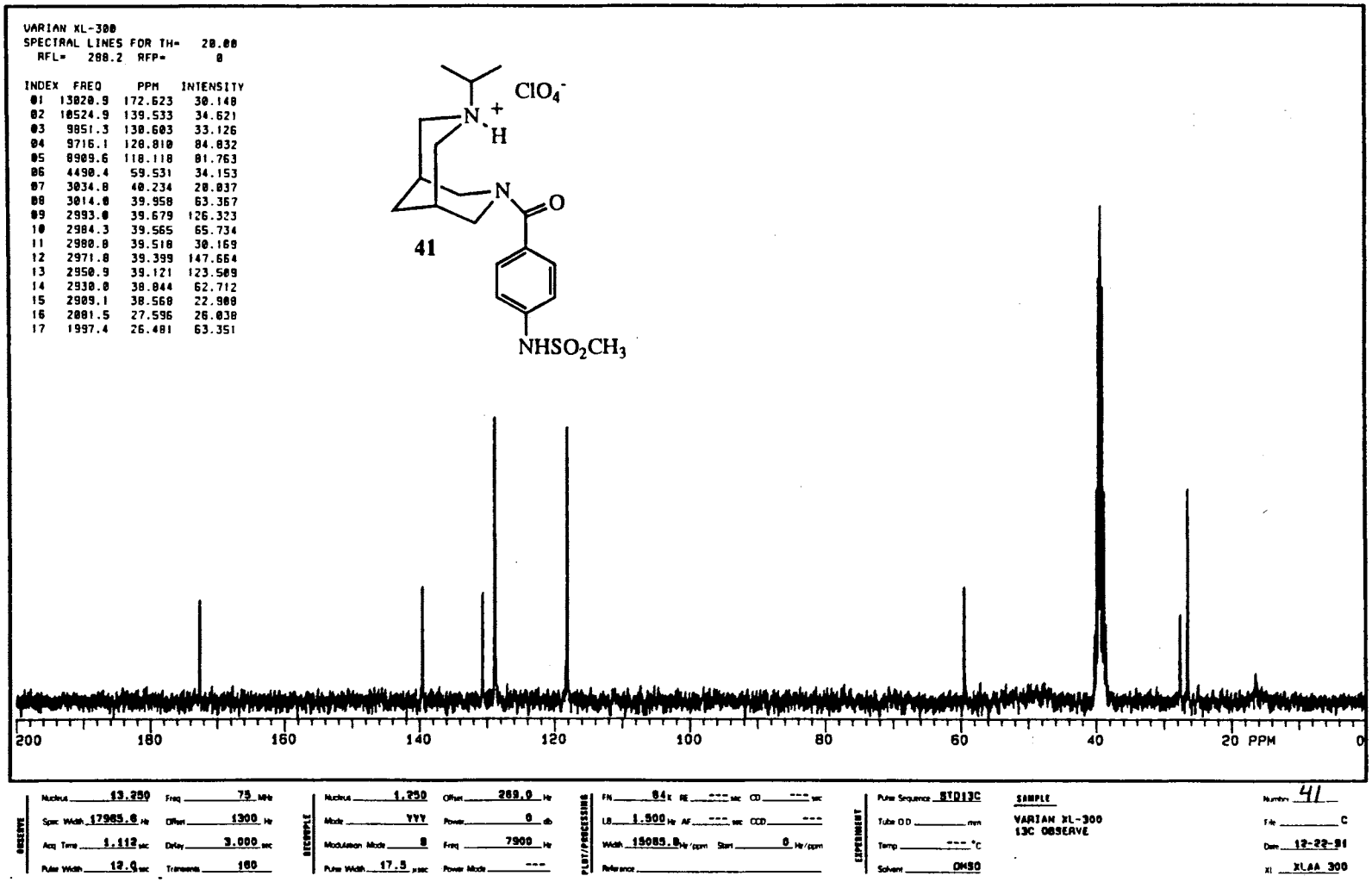
IR Spectrum of **41**

Plate XIII



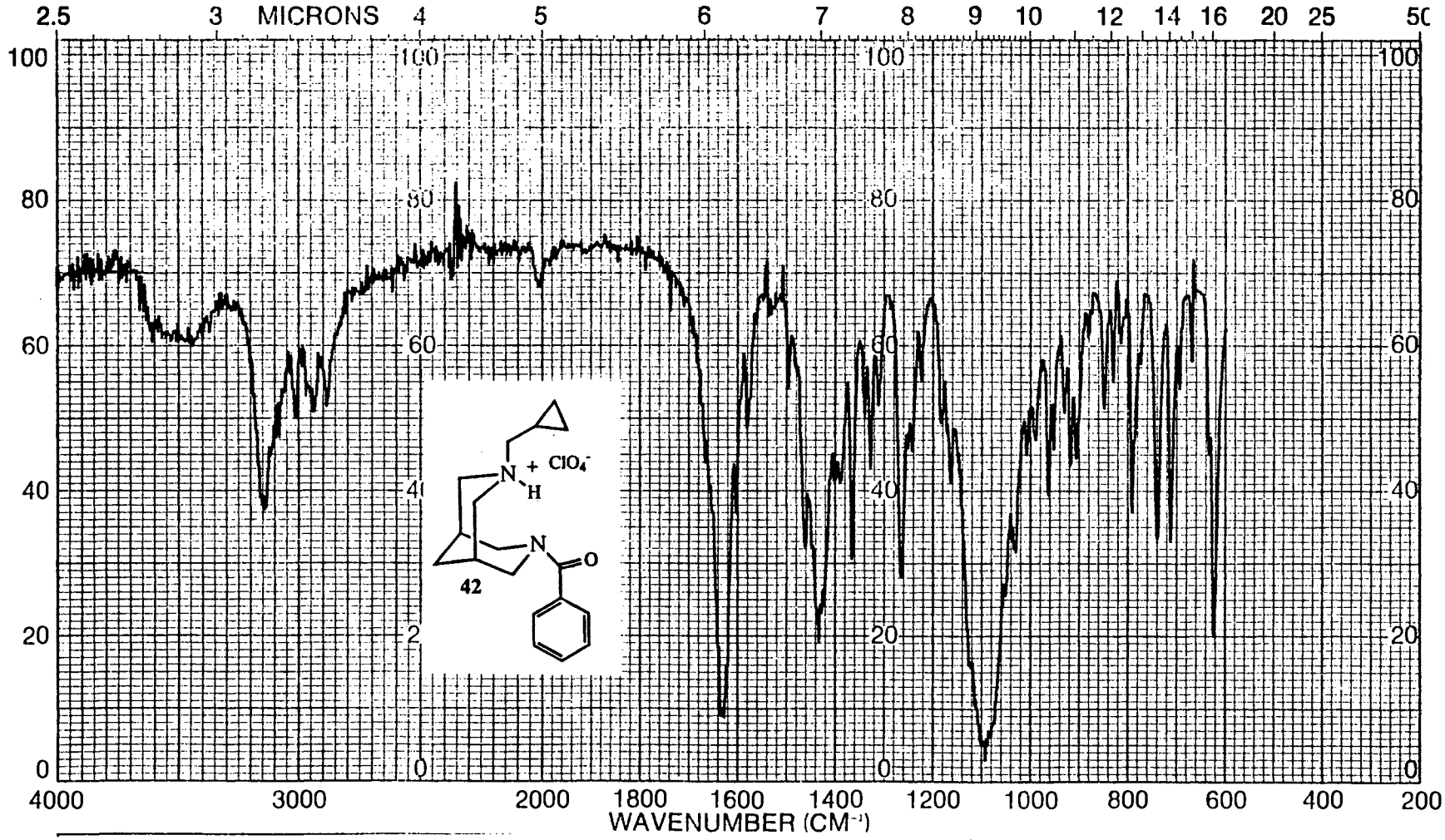
^{1}H NMR Spectrum of **41**

Plate XIV



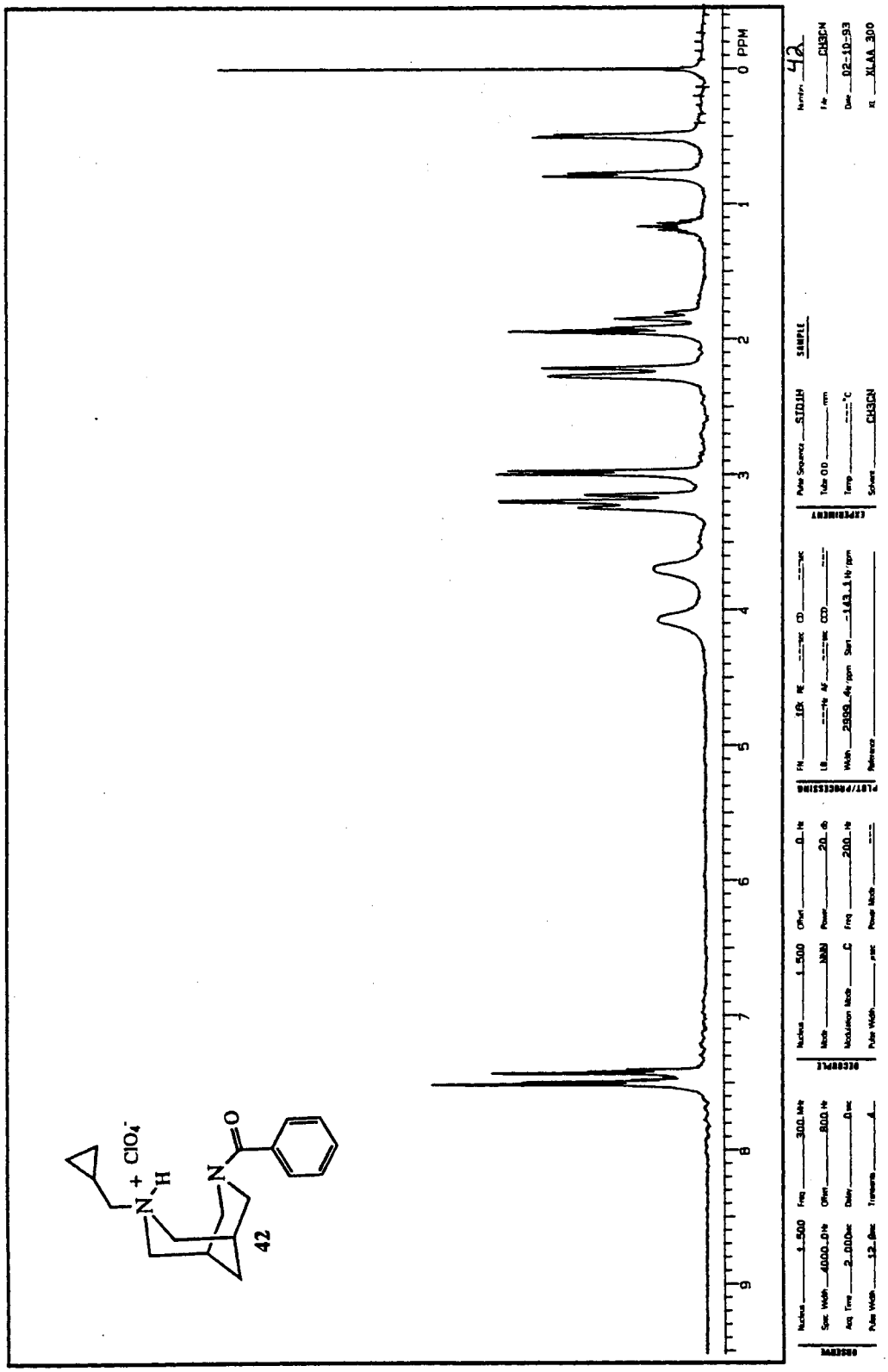
^{13}C NMR Spectrum of **41**

Plate XV



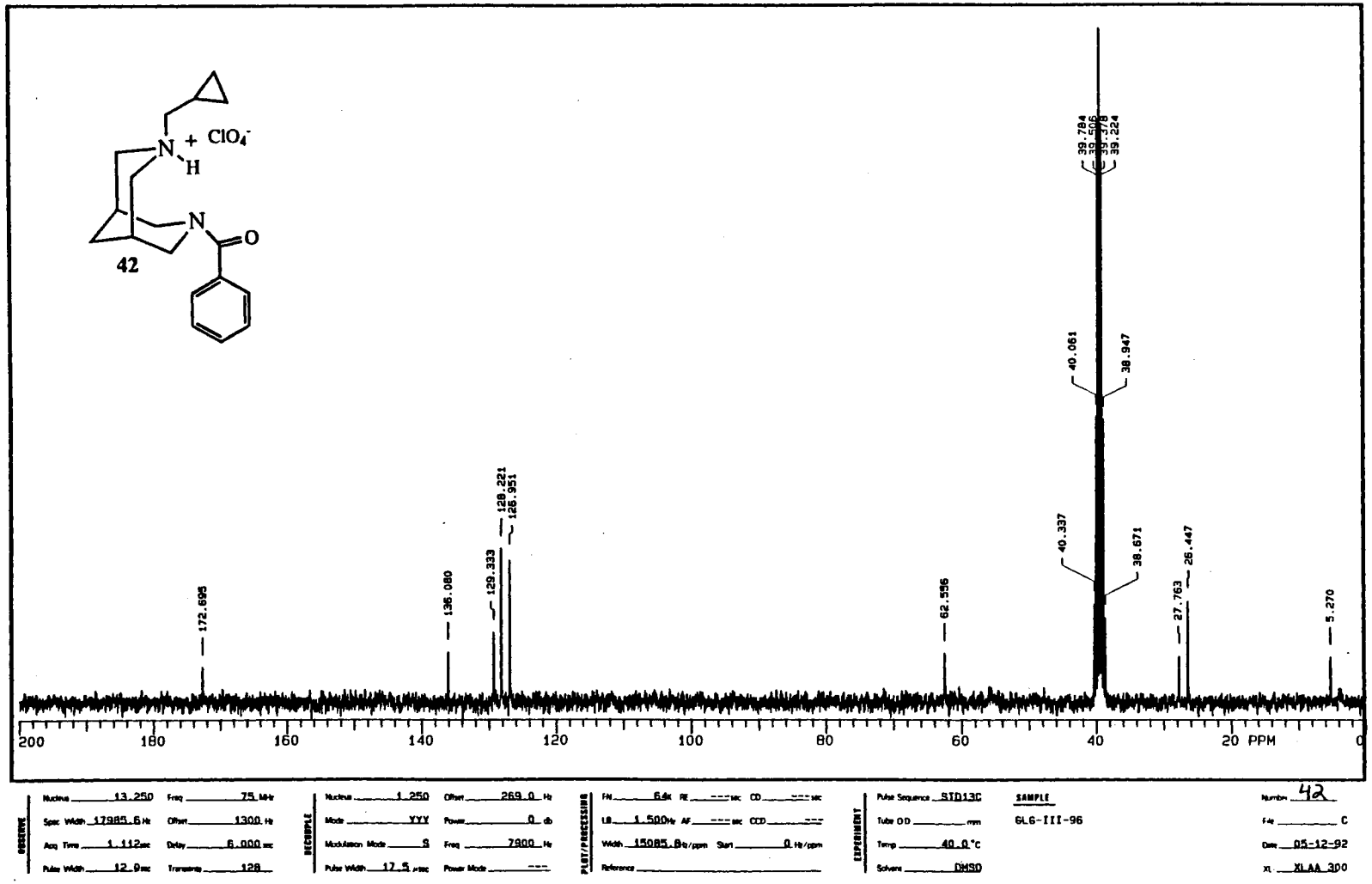
IR Spectrum of **42**

Plate XVI



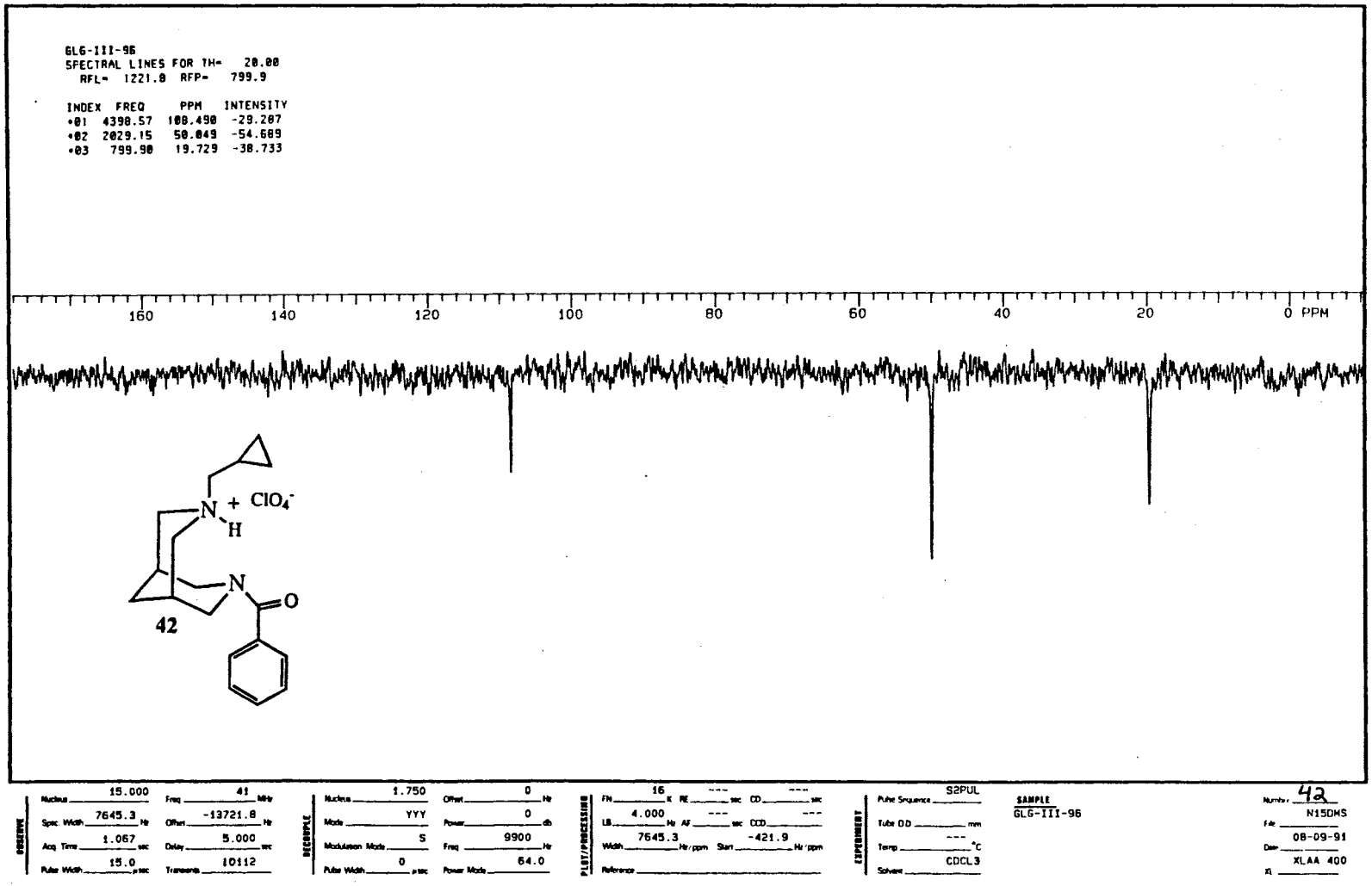
^{1}H NMR Spectrum of **42**

Plate XVII



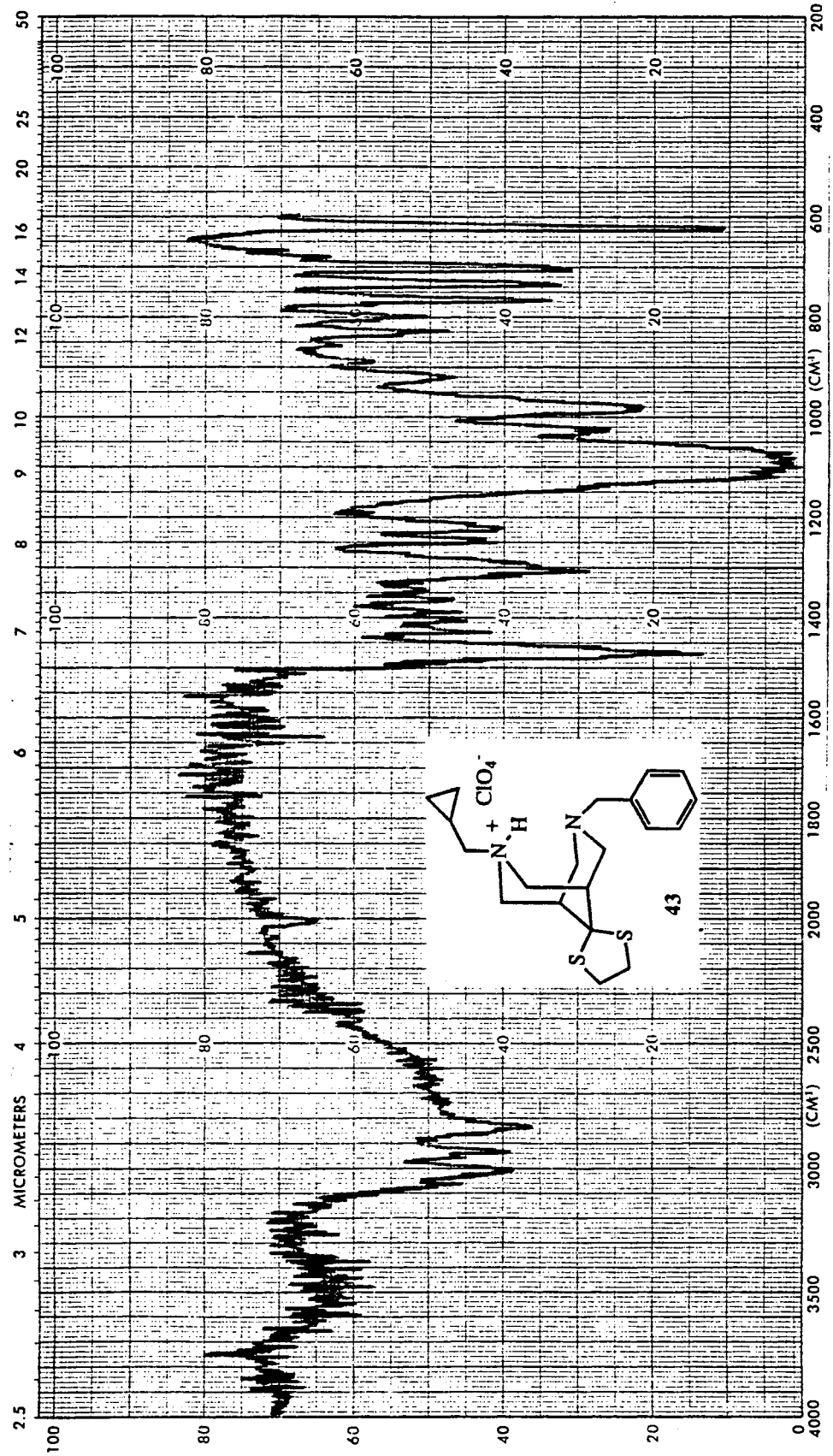
^{13}C NMR Spectrum of **42**

Plate XVIII



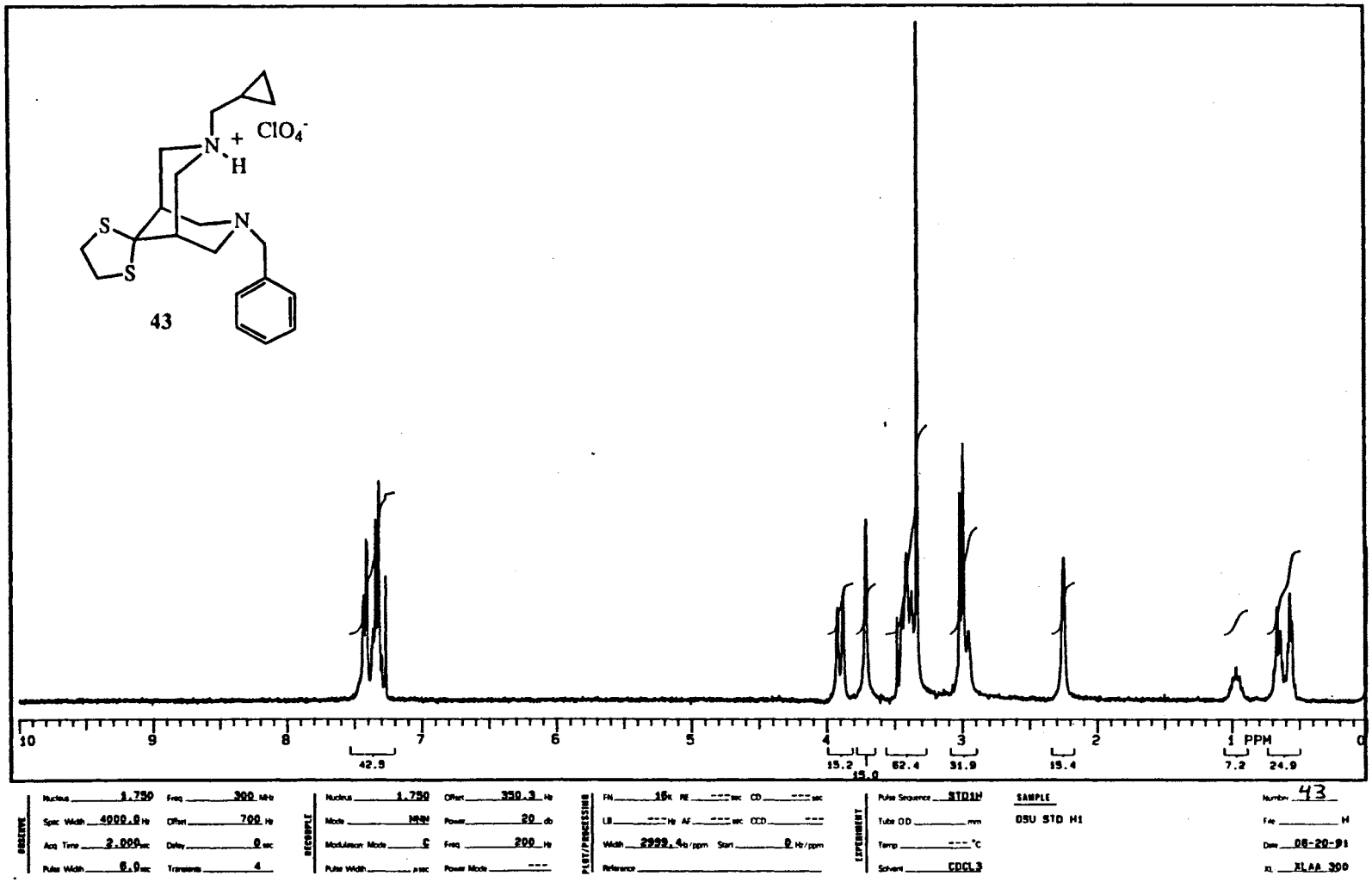
^{15}N NMR Spectrum of **42**

Plate XIX



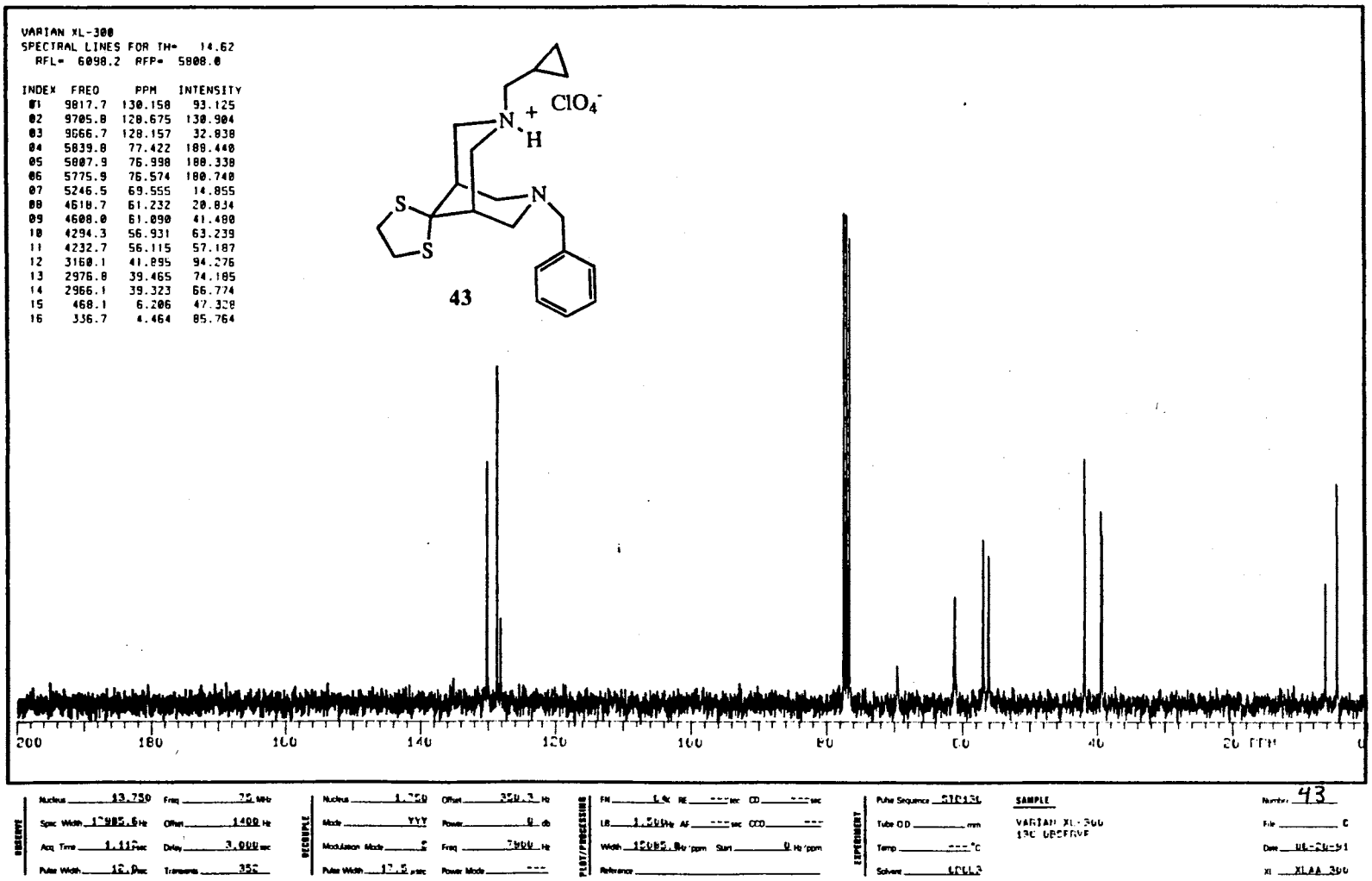
IR Spectrum of **43**

Plate XX



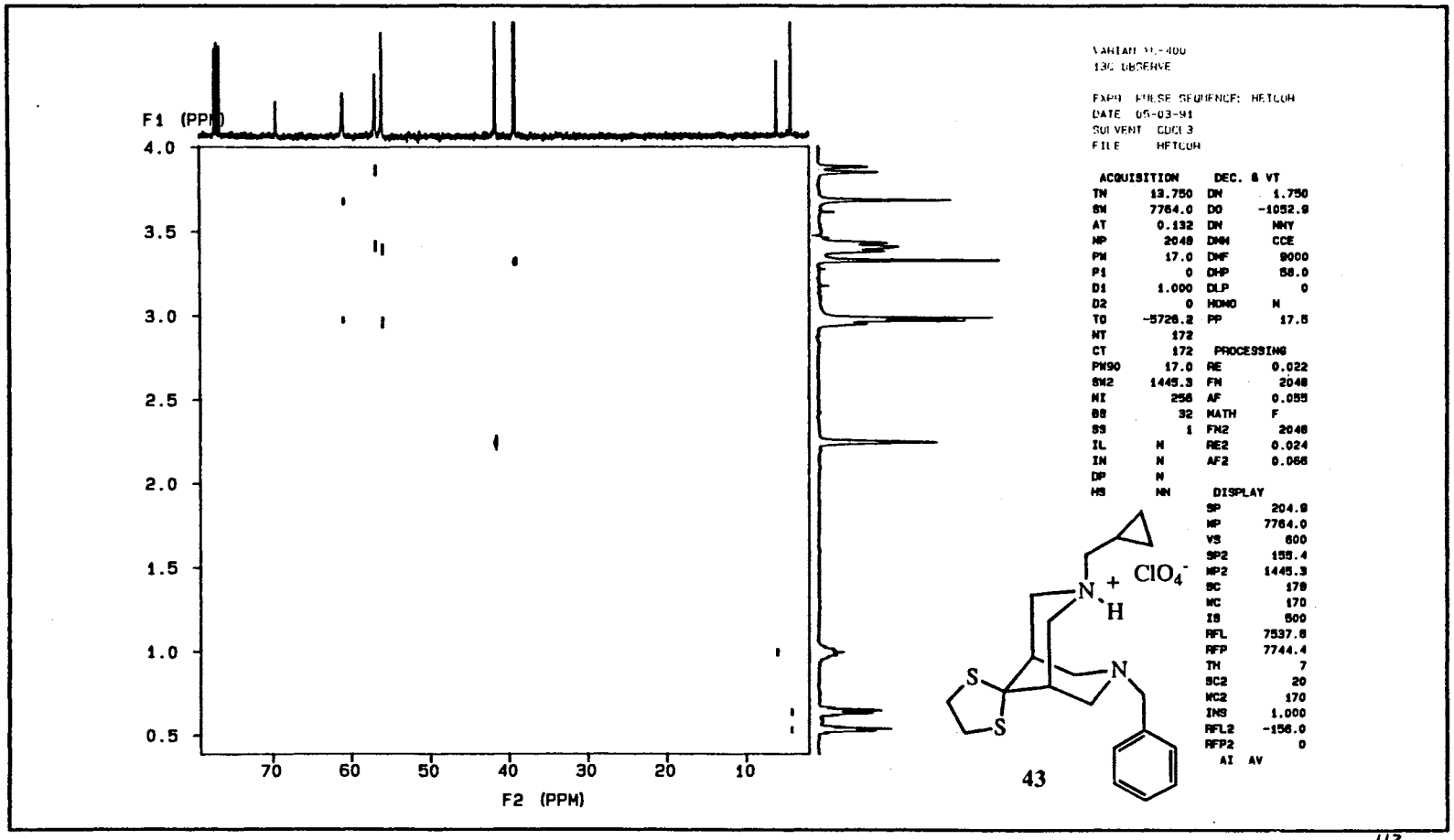
^{1}H NMR Spectrum of **43**

Plate XXI



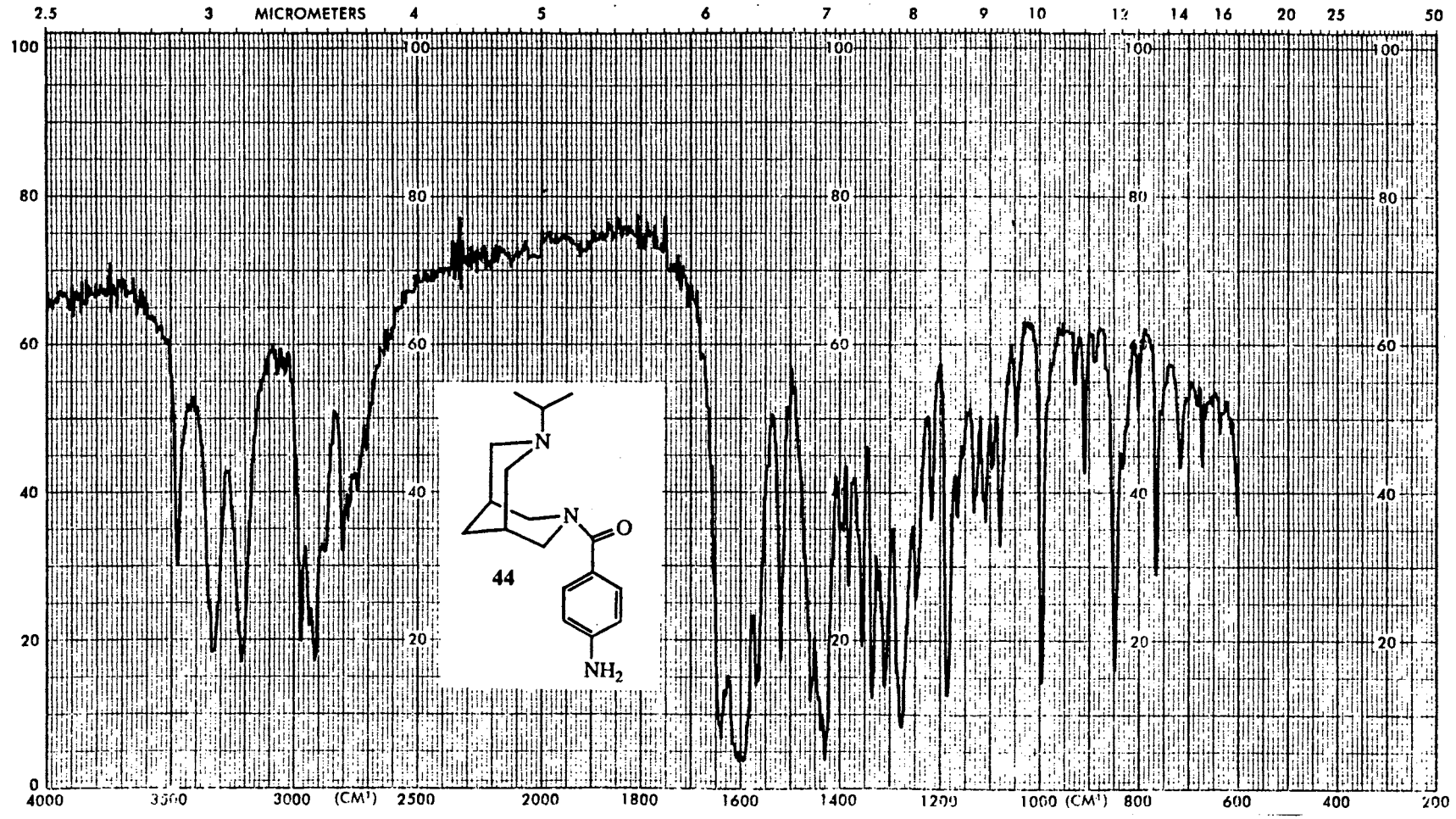
^{13}C NMR Spectrum of **43**

Plate XXII



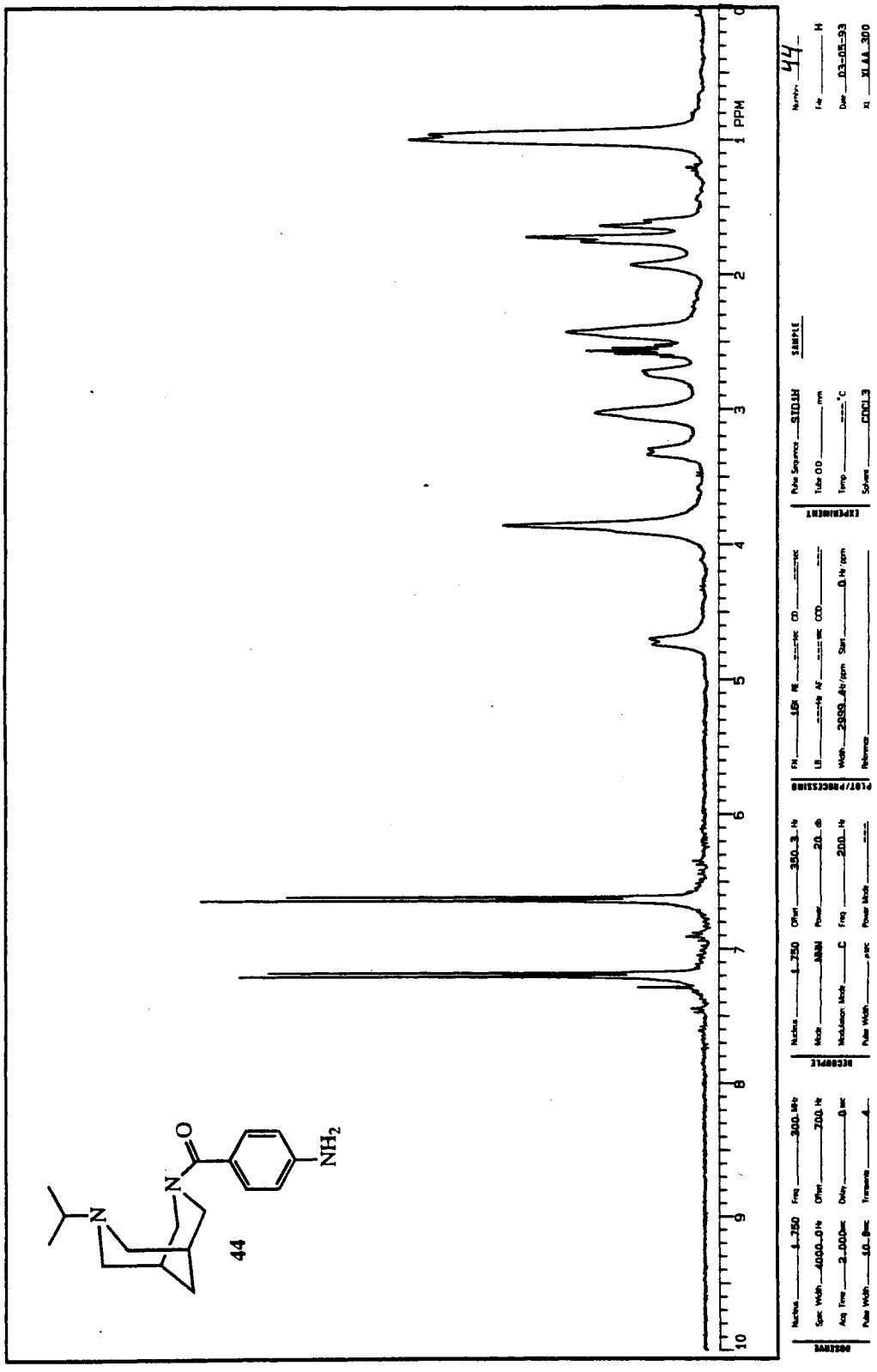
HETCOR Spectrum of **43**

Plate XXIII



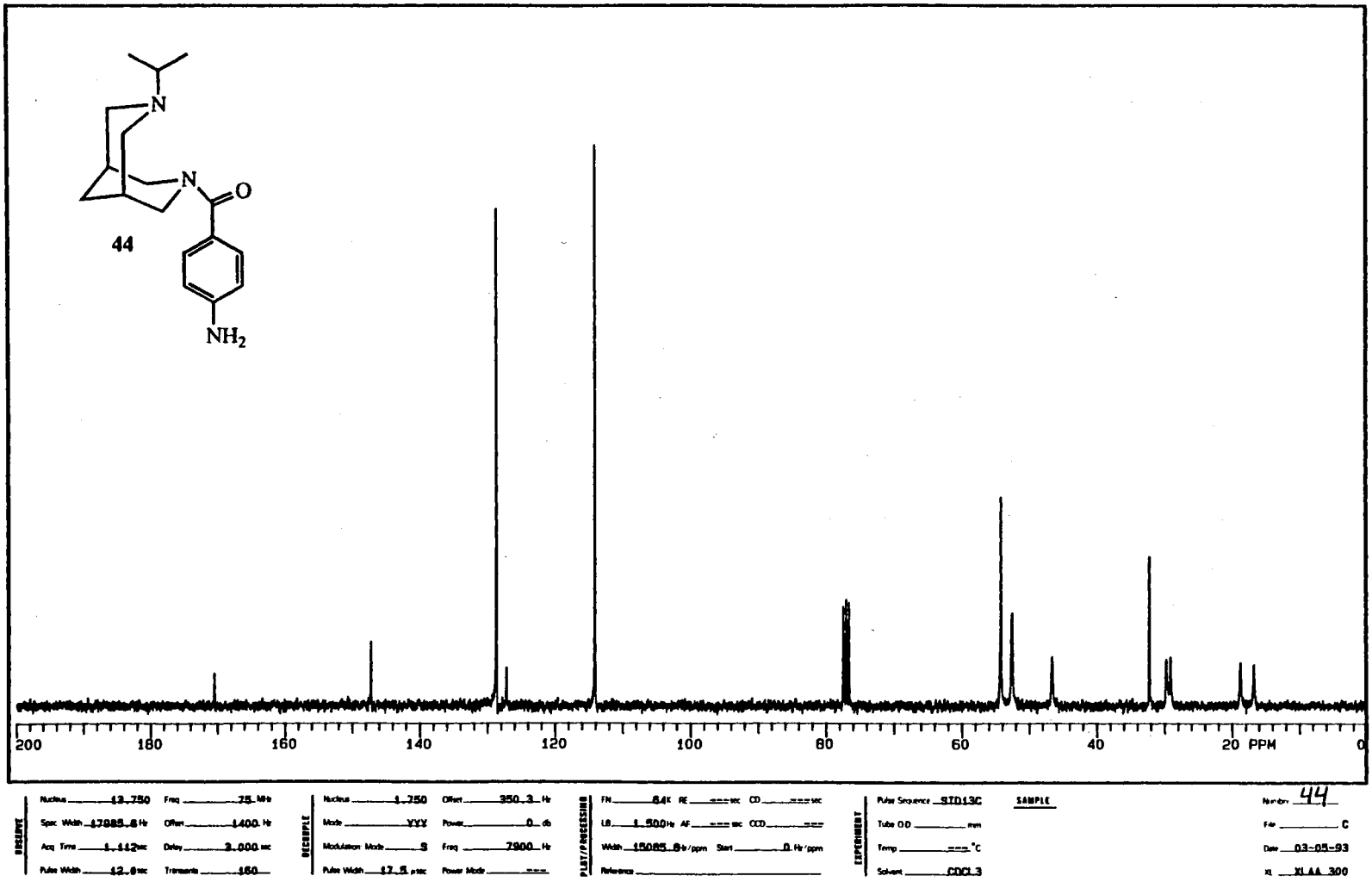
IR Spectrum of **44**

Plate XXIV



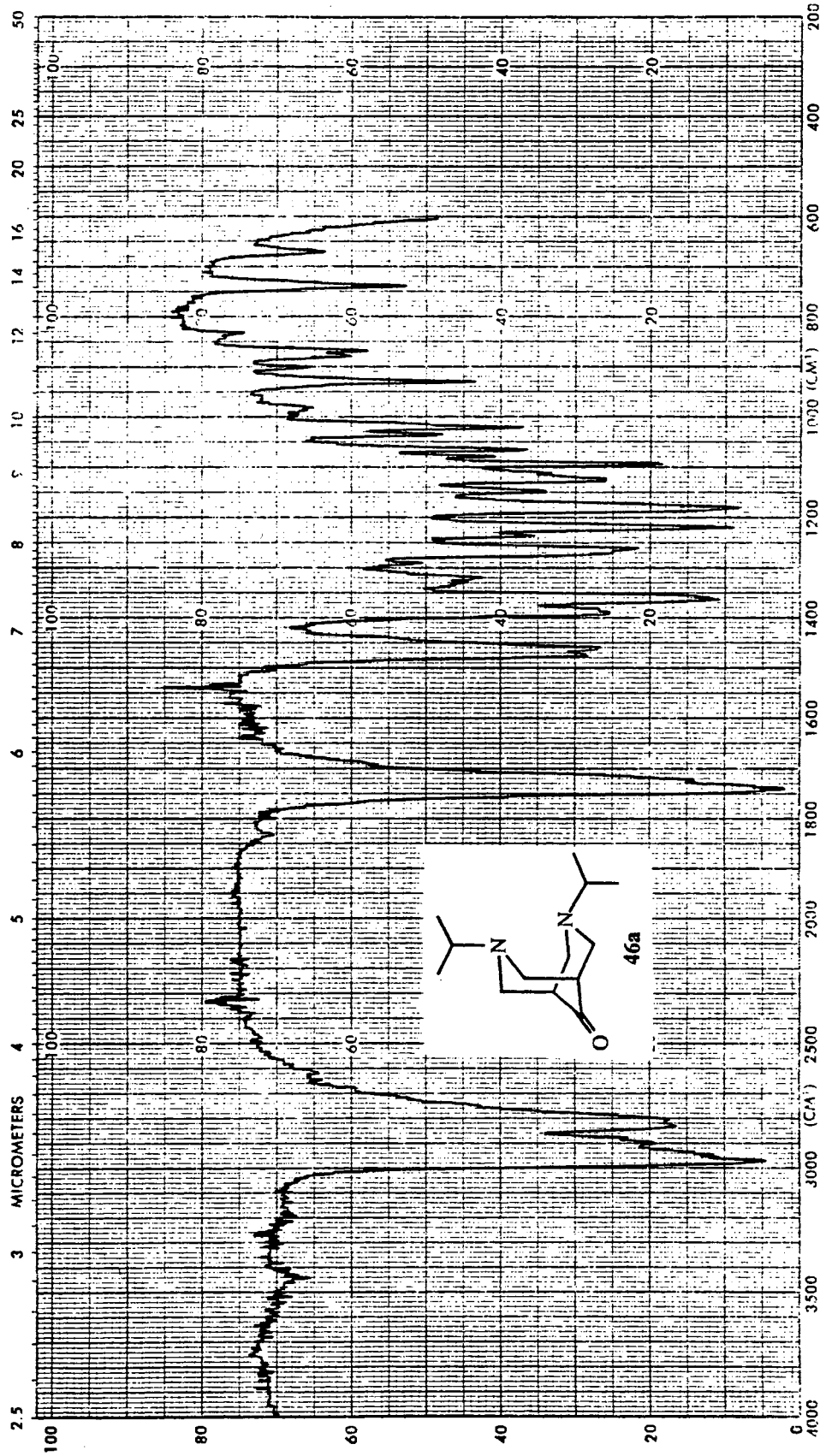
^{1}H NMR Spectrum of **44**

Plate XXV



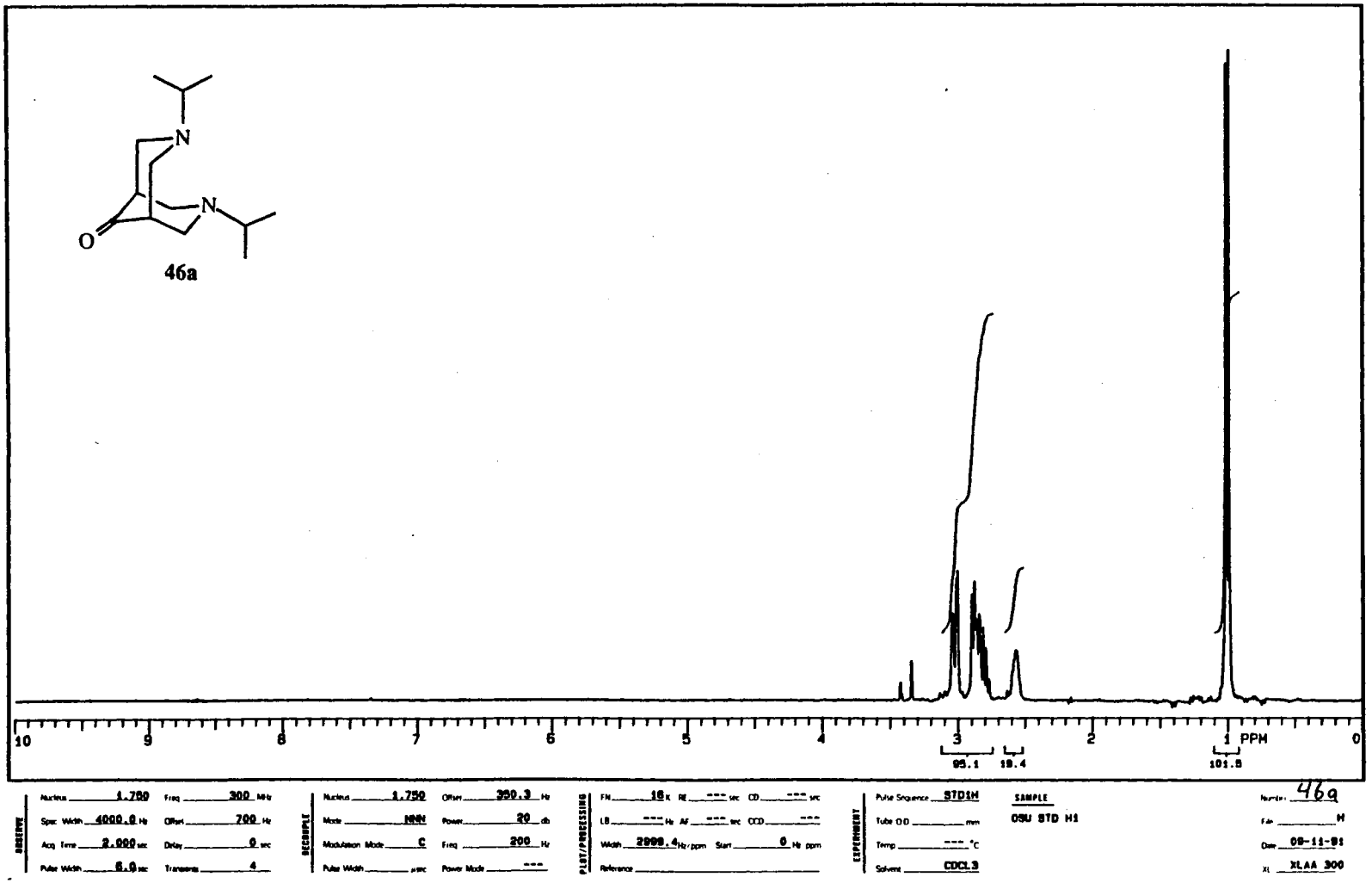
^{13}C NMR Spectrum of **44**

Plate XXVI



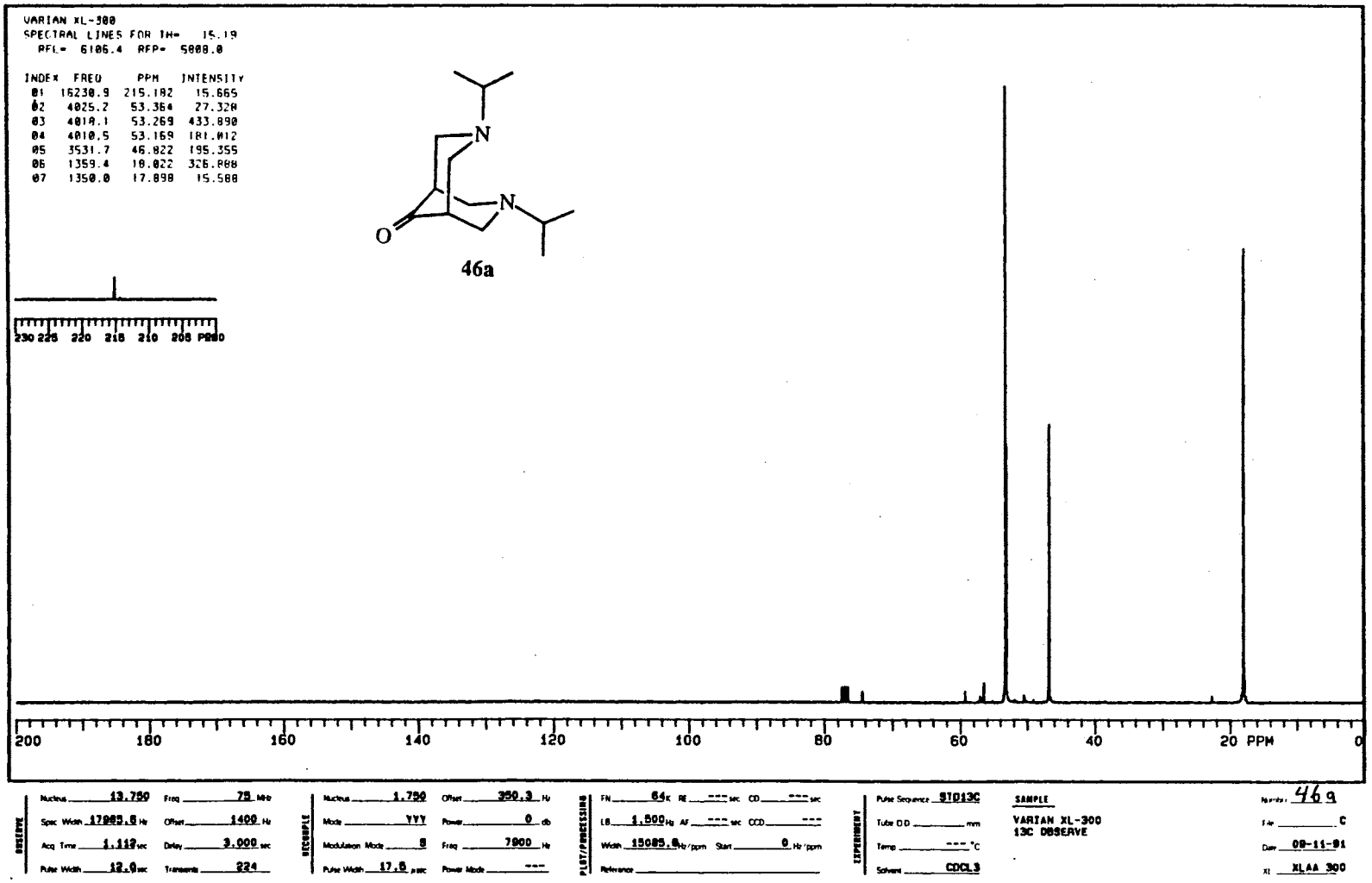
IR Spectrum of **46a**

Plate XXVII



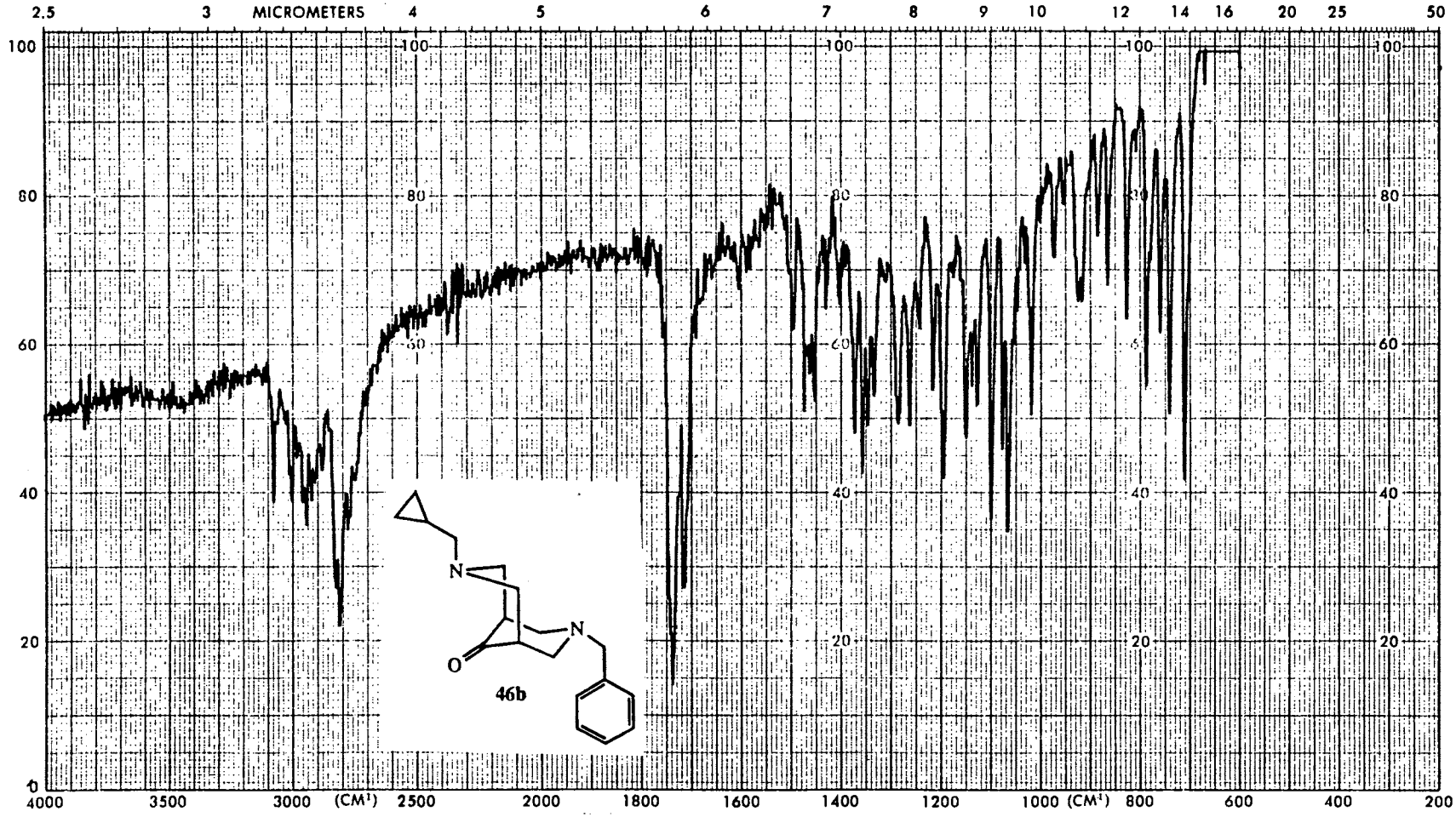
^{1}H NMR Spectrum of **46a**

Plate XXVIII



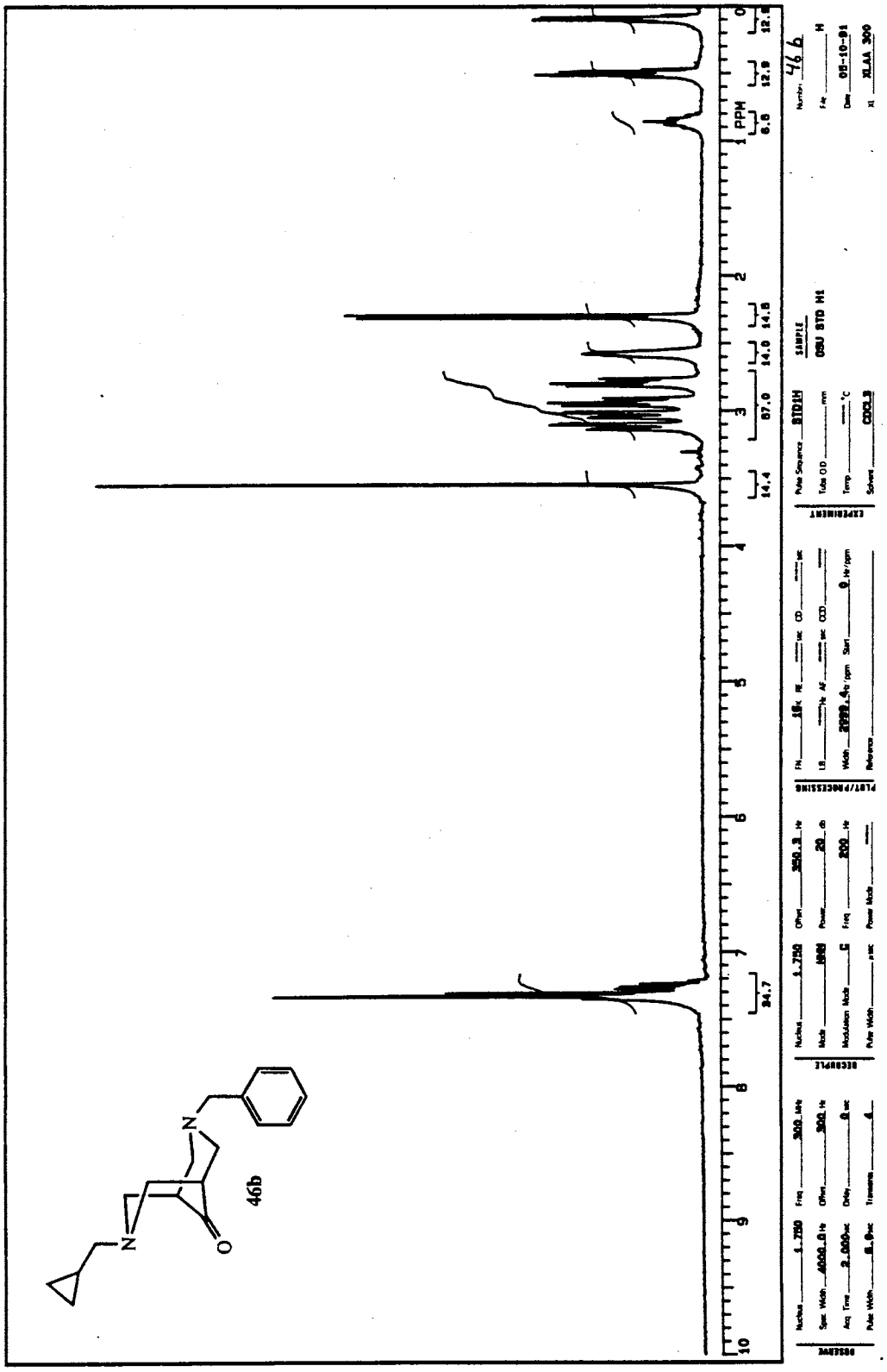
^{13}C NMR Spectrum of **46a**

Plate XXIX



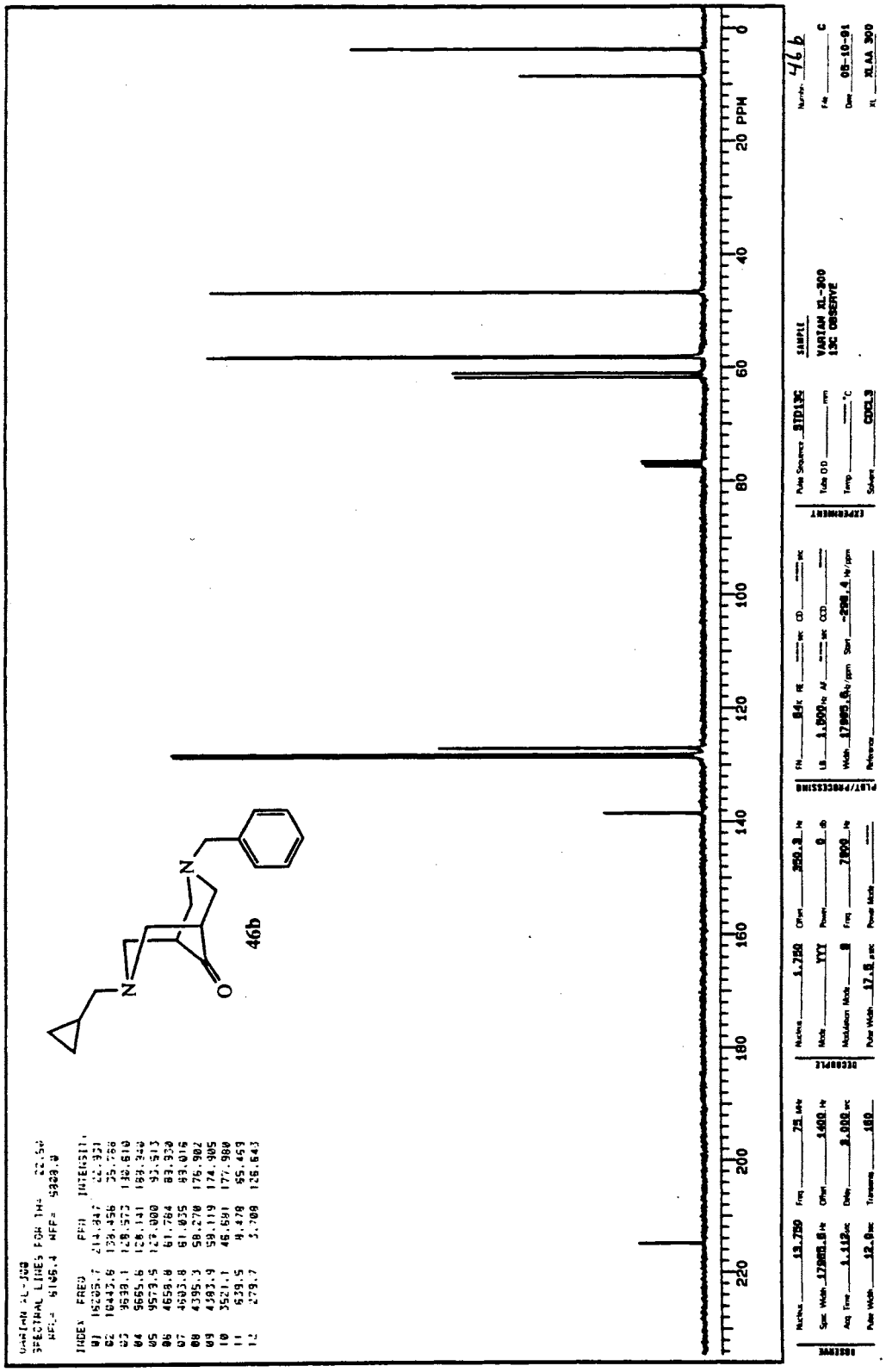
IR Spectrum of **46b**

Plate XXX



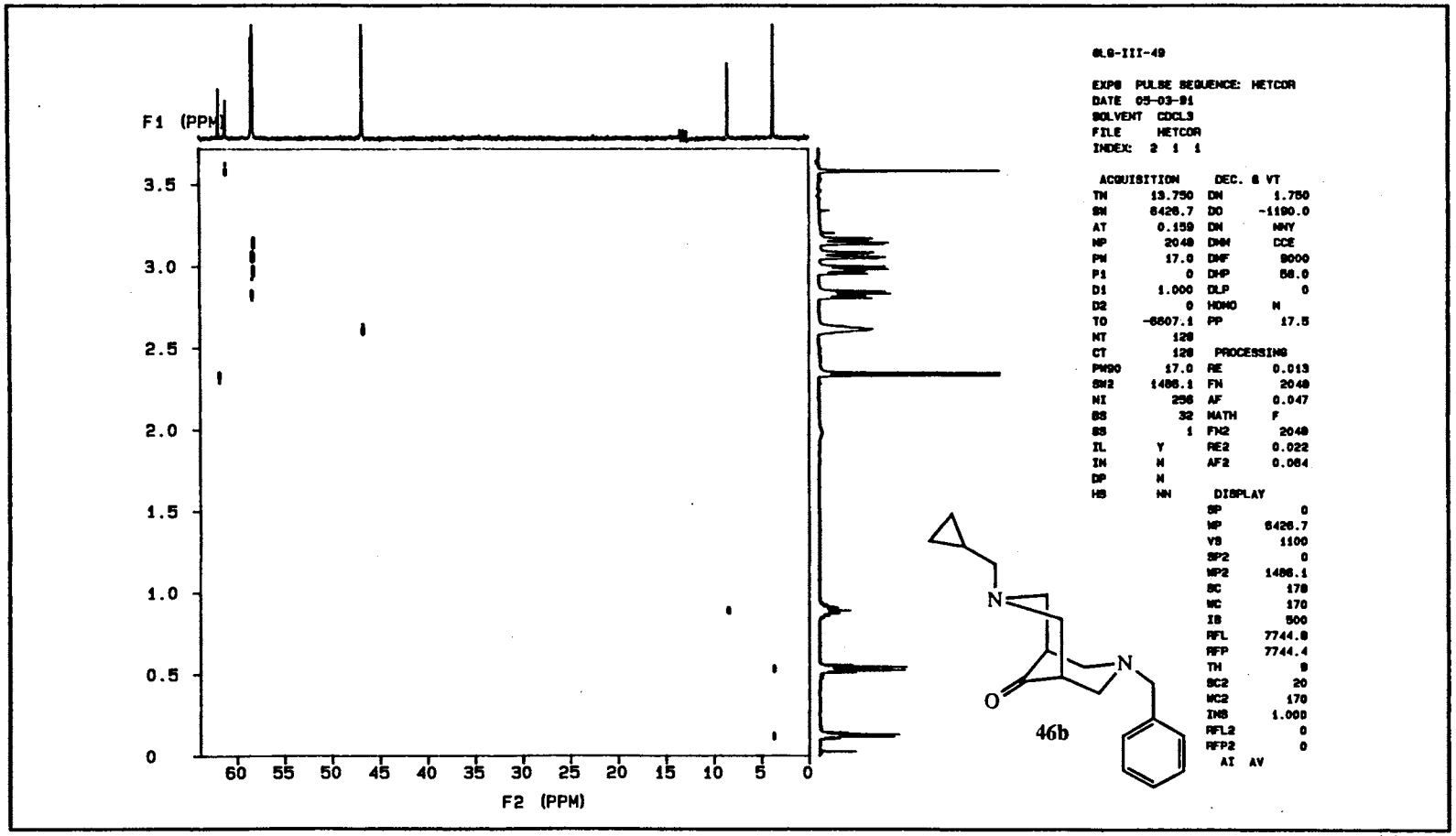
^{1}H NMR Spectrum of **46b**

Plate XXXI



^{13}C NMR Spectrum of **46b**

Plate XXXII



OBSERVE Nucleus ____ Freq ____ MHz; Spec Width ____ Hz Offset ____ Hz; Acq Time ____ sec Delay ____ sec; Pulse Width ____ μsec Transmit ____

DECOUPLE Nucleus ____ Offset ____ Hz; Mode ____ Power ____ db; Mod/Ason Mode ____ Freq ____ Hz; Pulse Width ____ μsec Power Mode ____

PLOT/PROCESSING FN ____ K RE ____ sec CD ____ sec; LB ____ Hz AF ____ sec CCD ____; Width ____ Hz/ppm Start ____ Hz/ppm; Reference ____

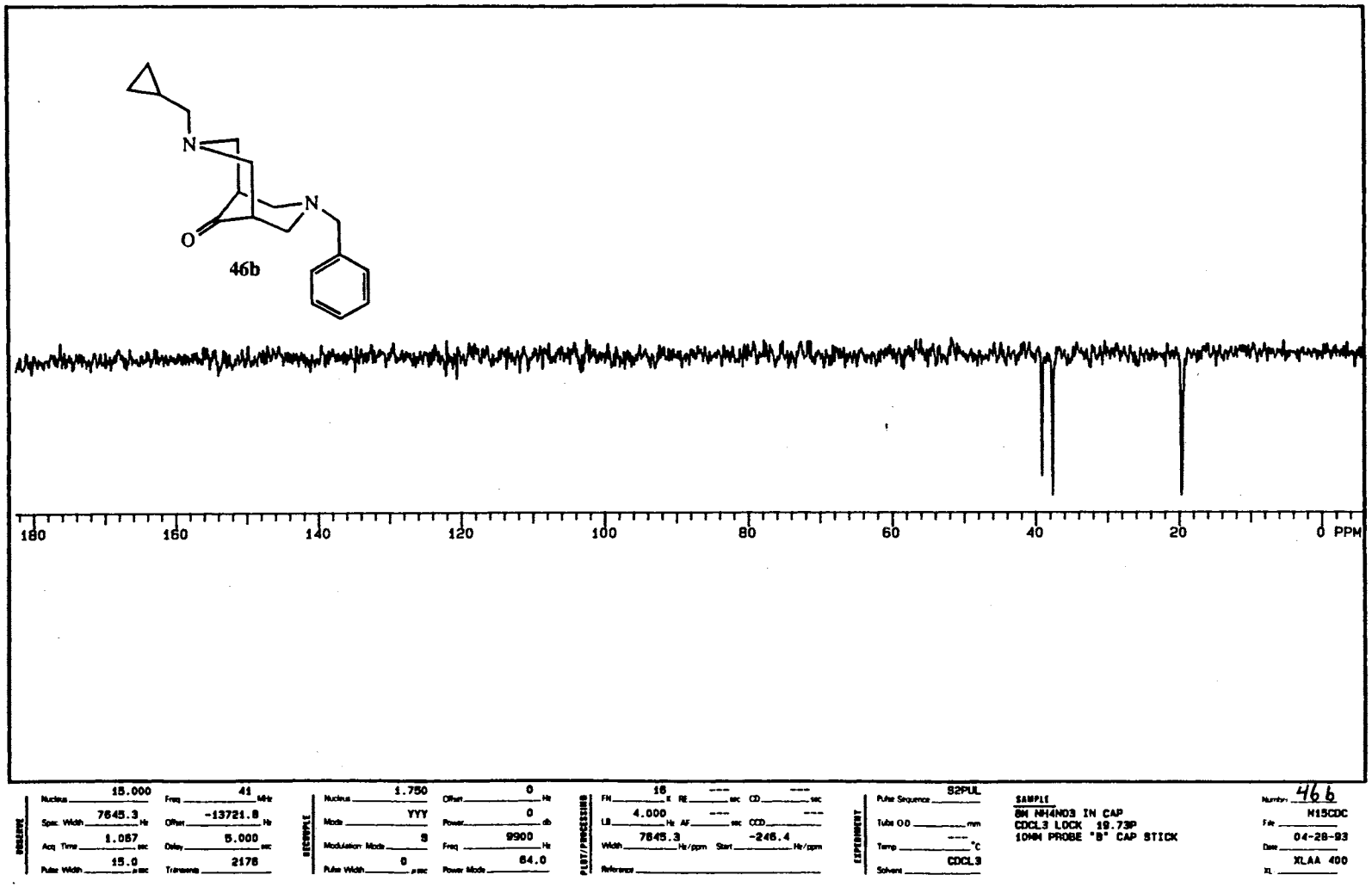
EXPERIMENT Pulse Sequence ____; Tube O.D. ____ mm; Temp ____ °C; Solvent ____

SAMPLE

Number 46b; File ____; Date ____; xl ____

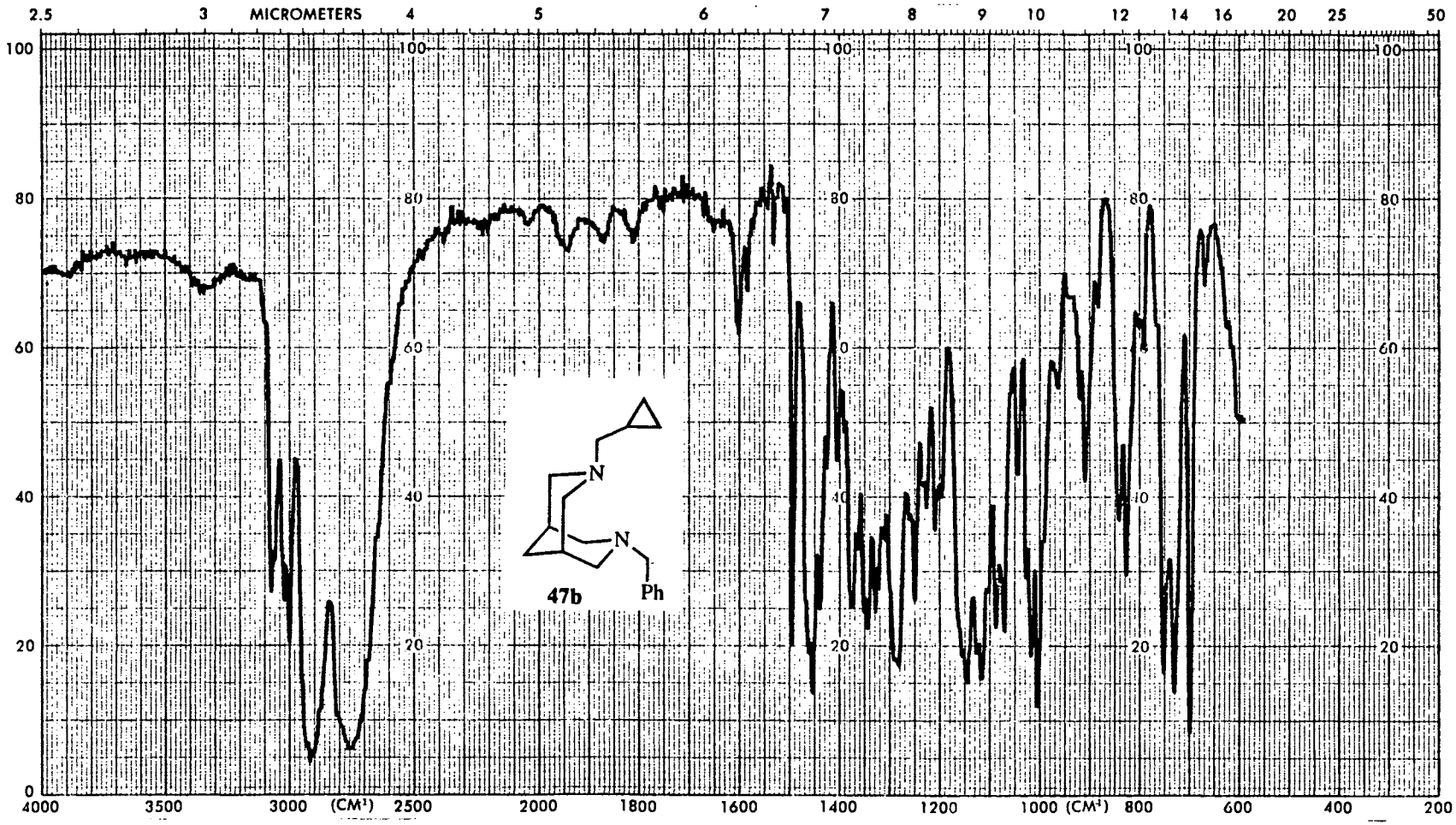
HETCOR Spectrum of **46b**

Plate XXXIII



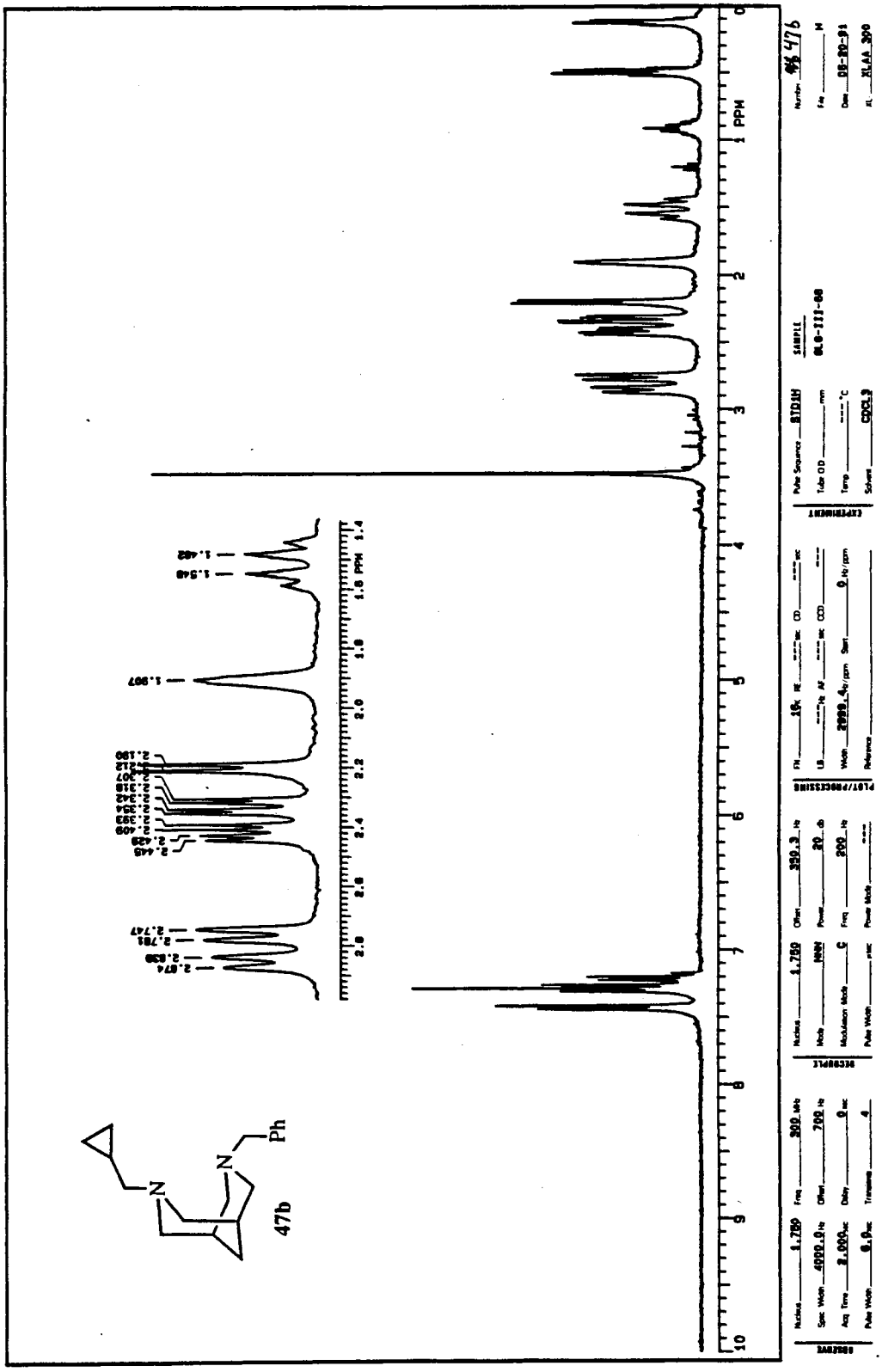
^{15}N NMR Spectrum of **46b**

Plate XXXIV



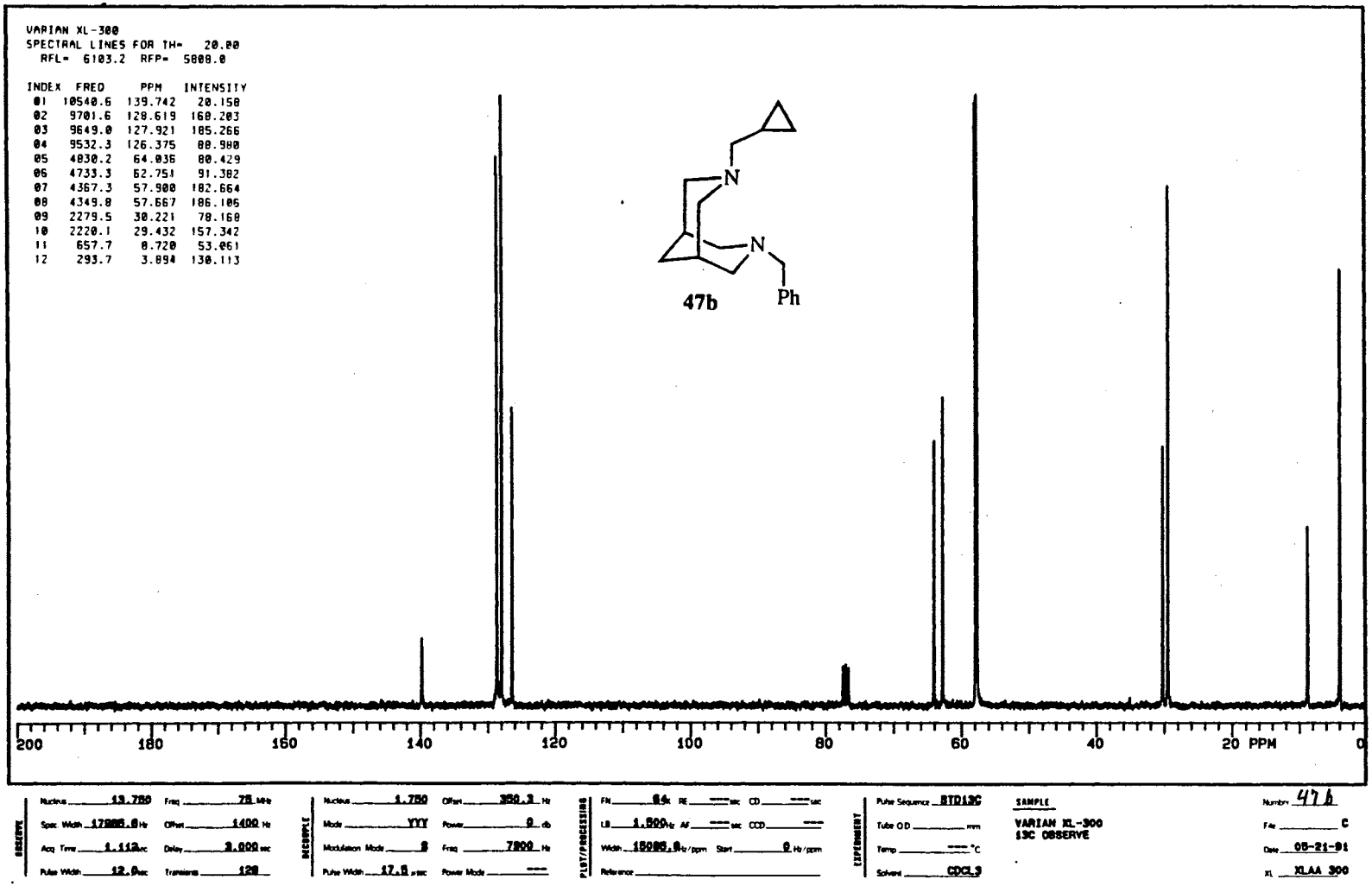
IR Spectrum of **47b**

Plate XXXV



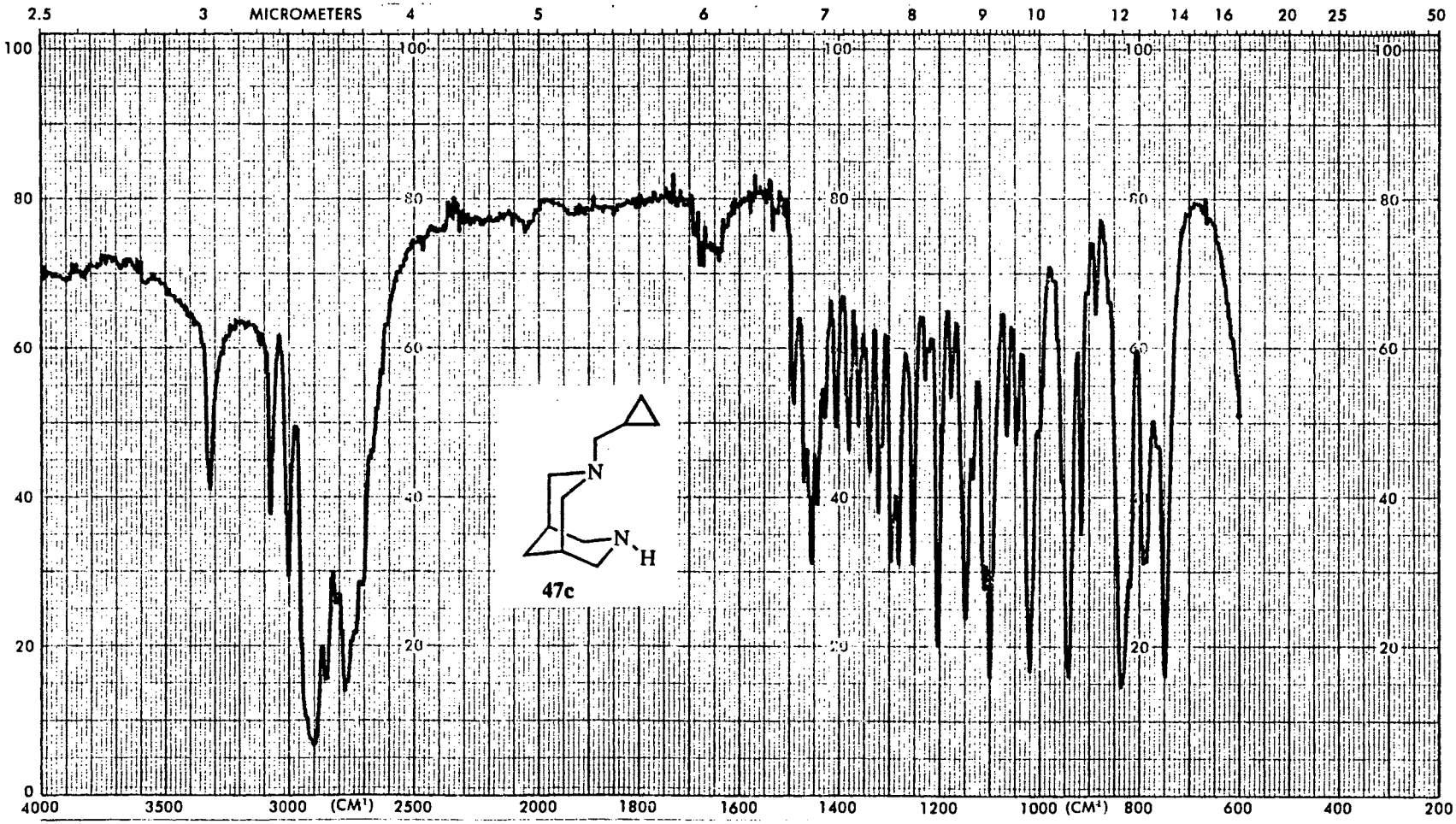
^{1}H NMR Spectrum of 47b

Plate XXXVI



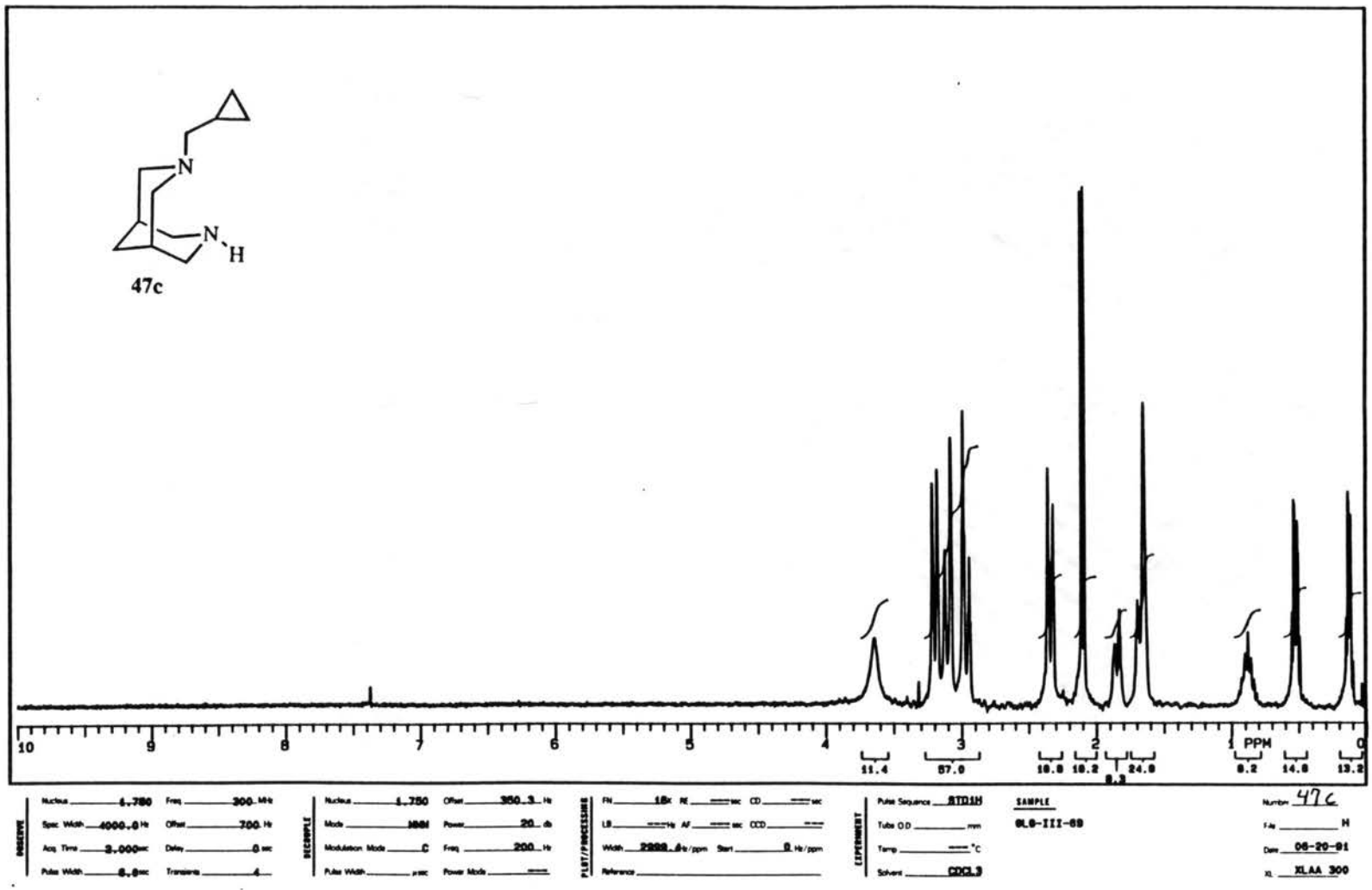
^{13}C NMR Spectrum of **47b**

Plate XXXVII



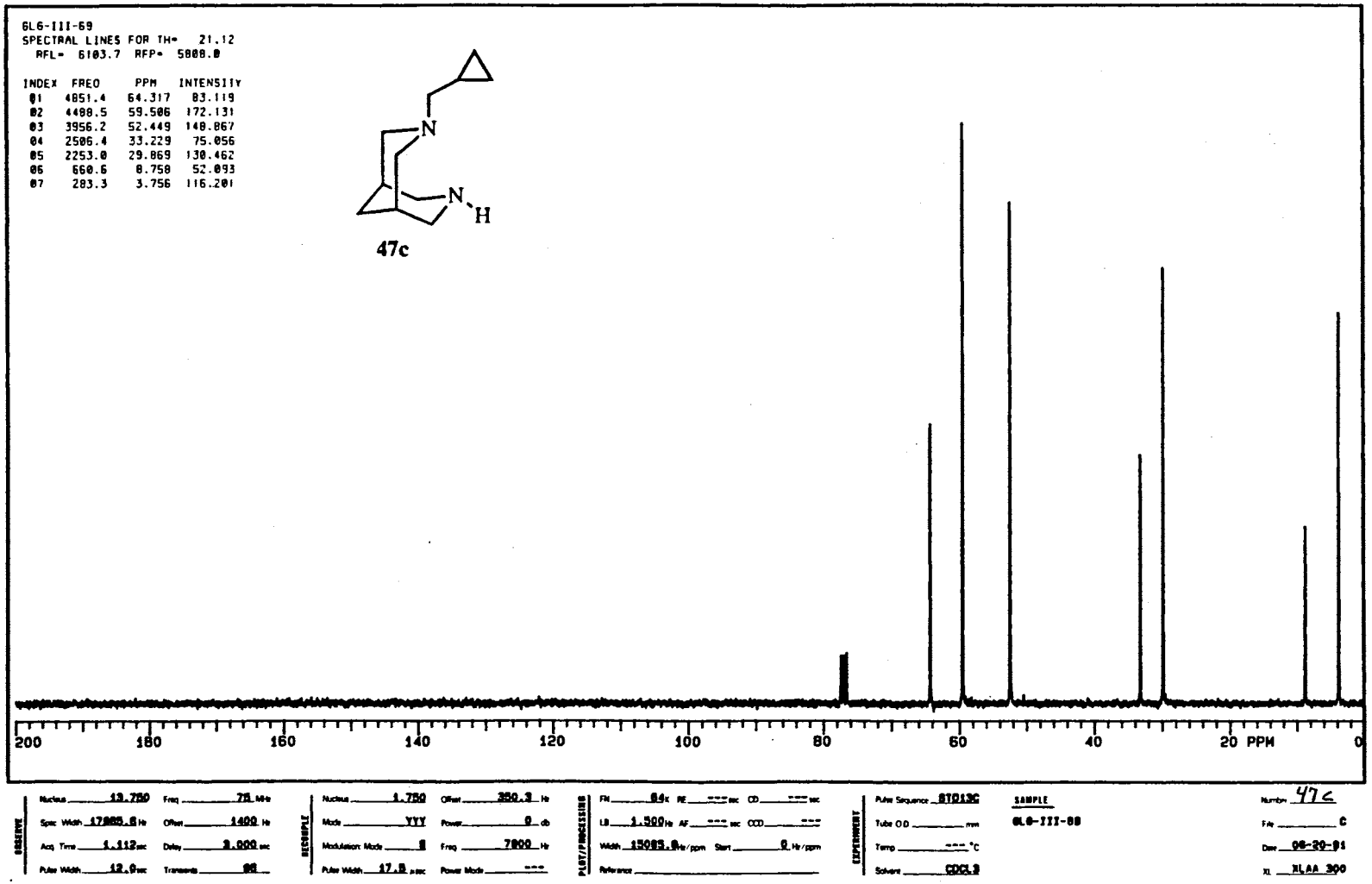
IR Spectrum of **47c**

Plate XXXVIII



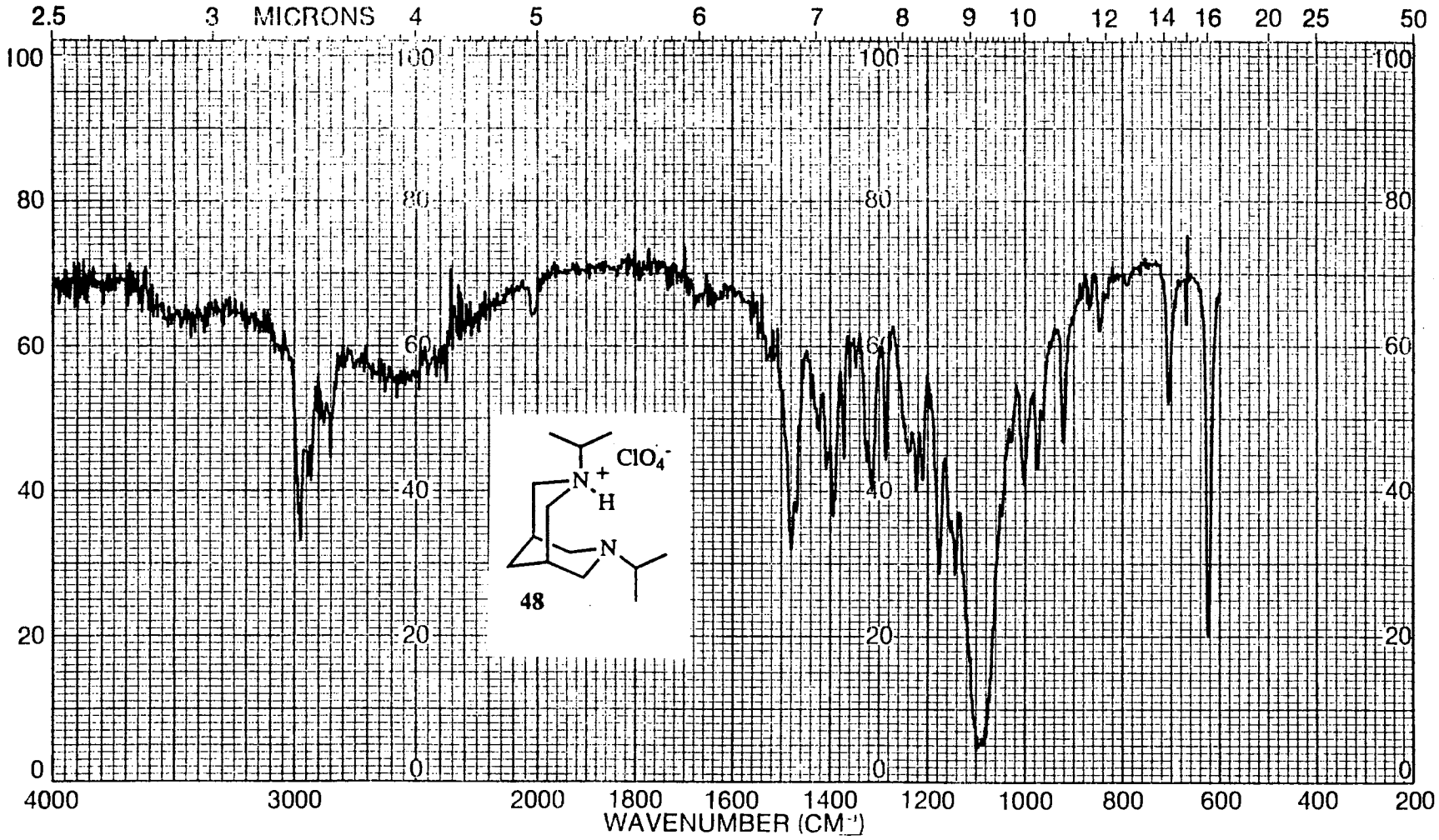
^{1}H NMR Spectrum of **47c**

Plate XXXIX



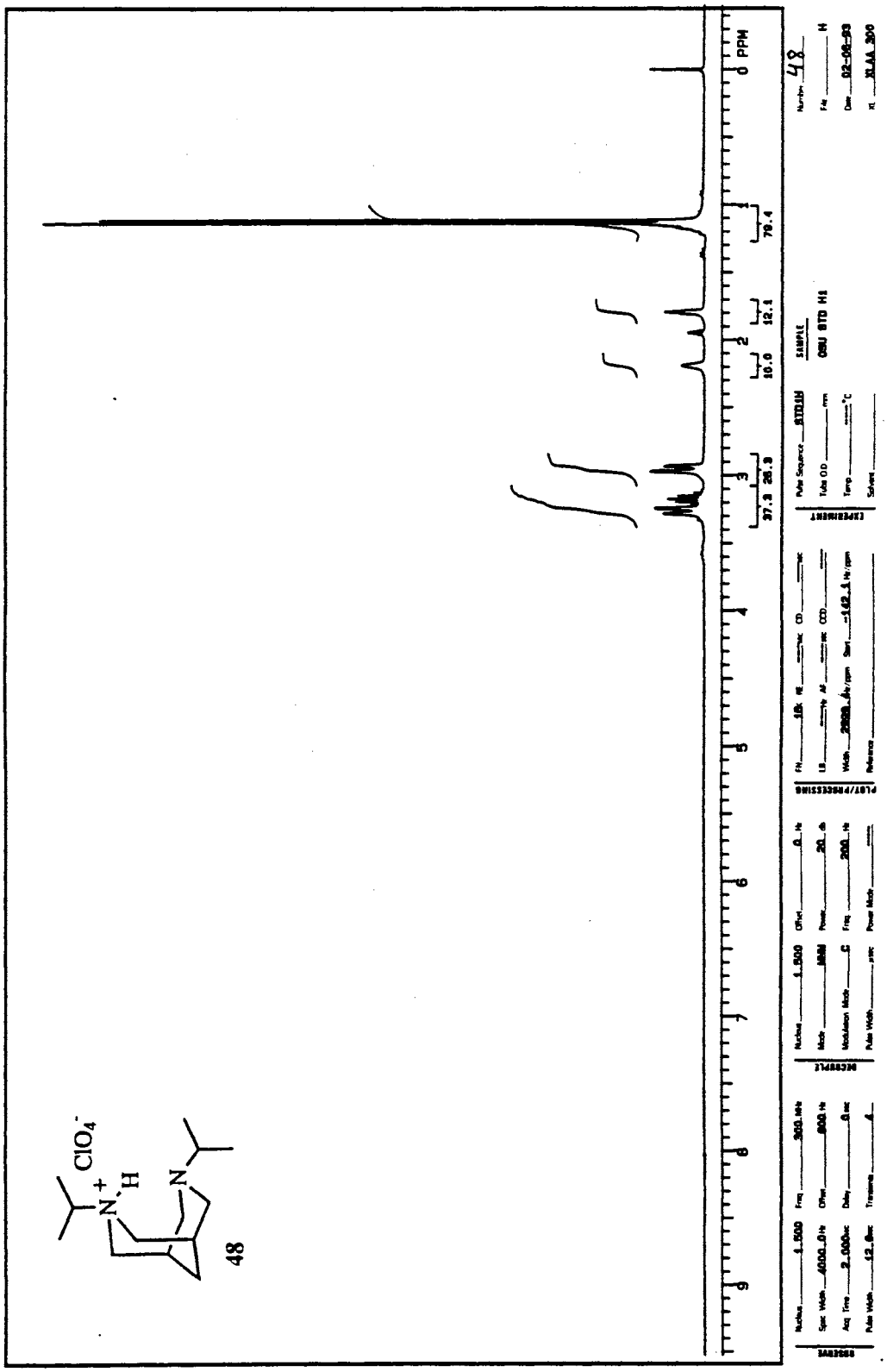
^{13}C NMR Spectrum of **47c**

Plate XL



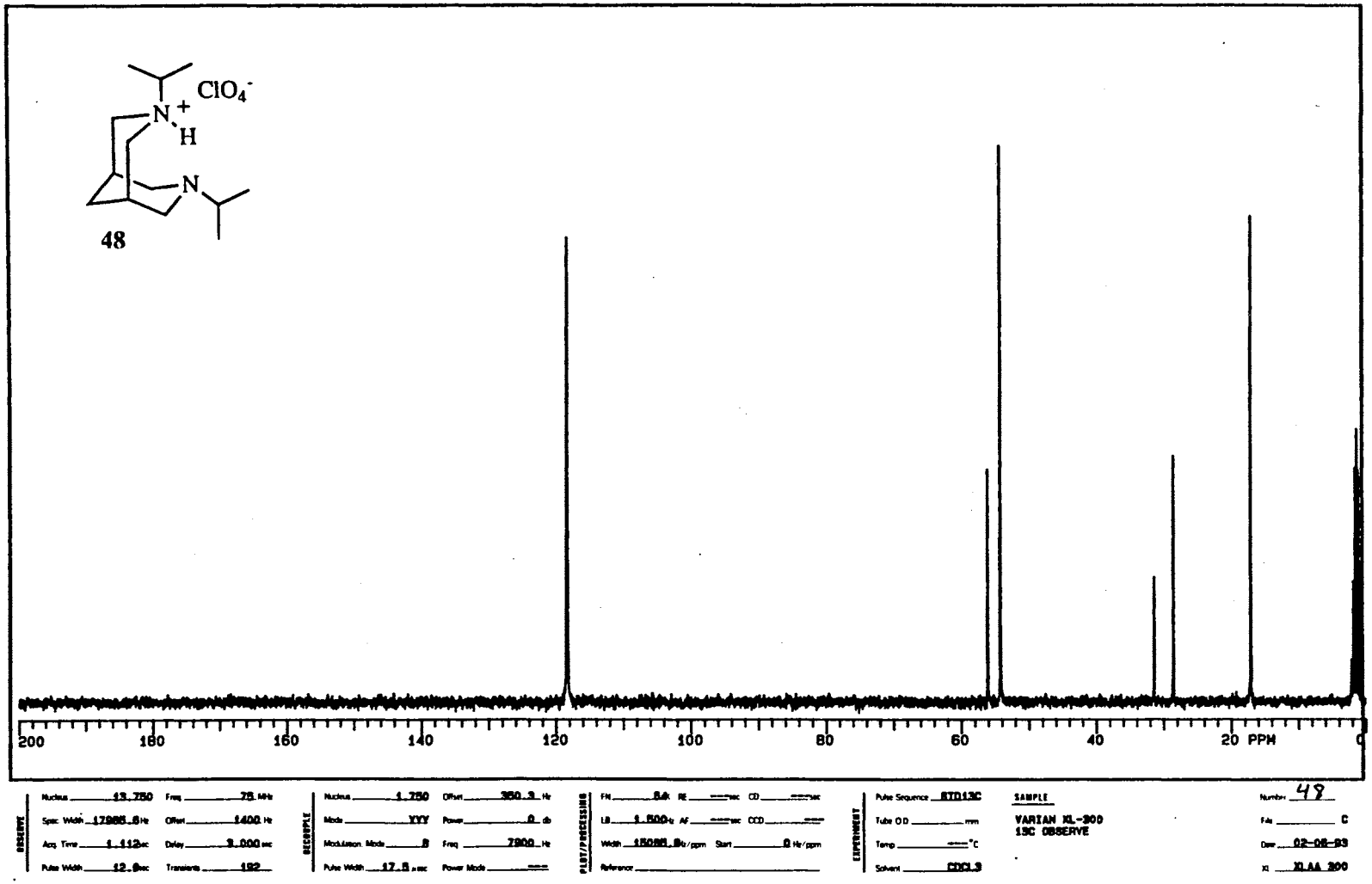
IR Spectrum of **48**

Plate XLI



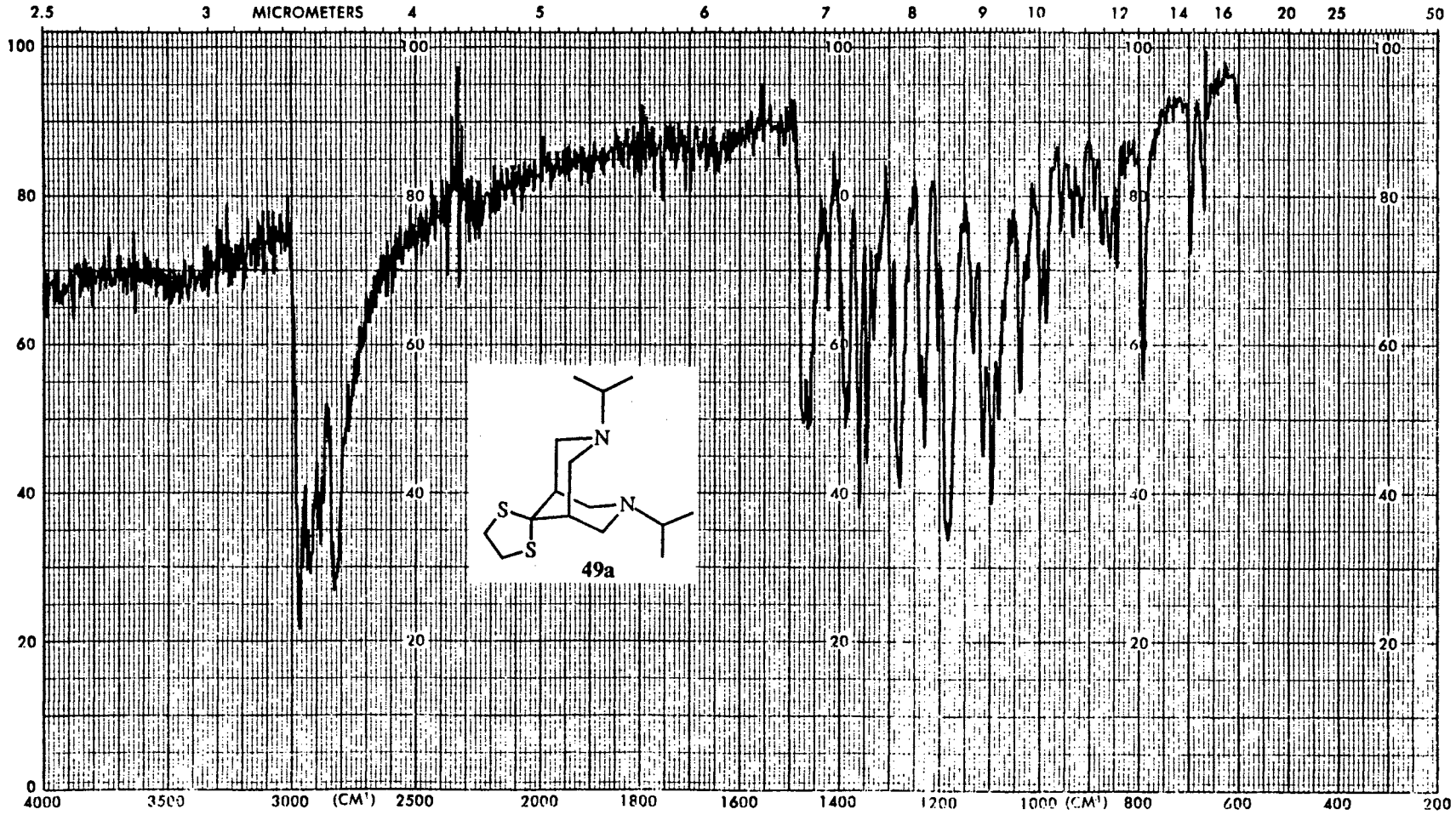
^{1}H NMR Spectrum of **48**

Plate XLII



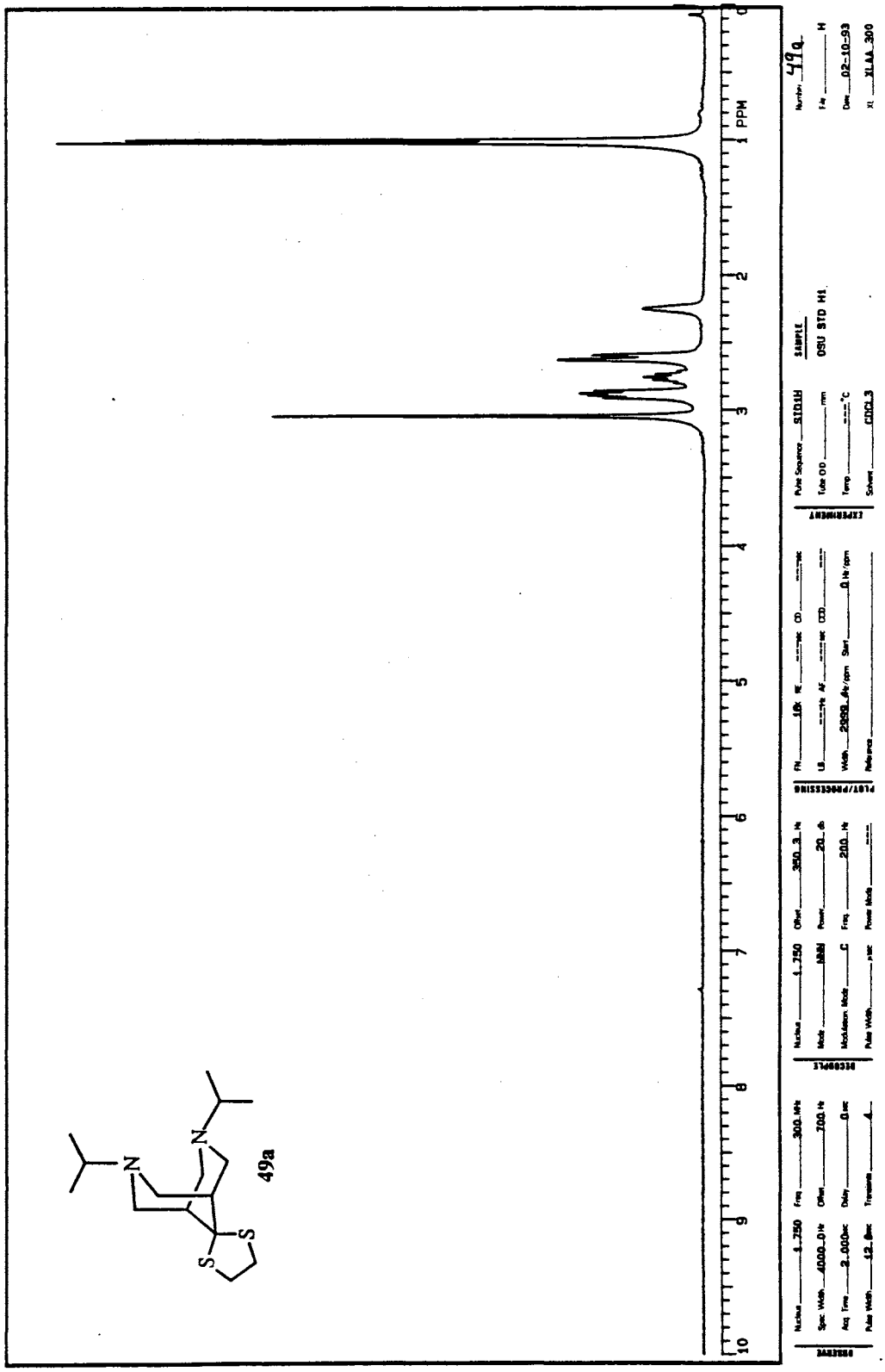
^{13}C NMR Spectrum of **48**

Plate XLIII



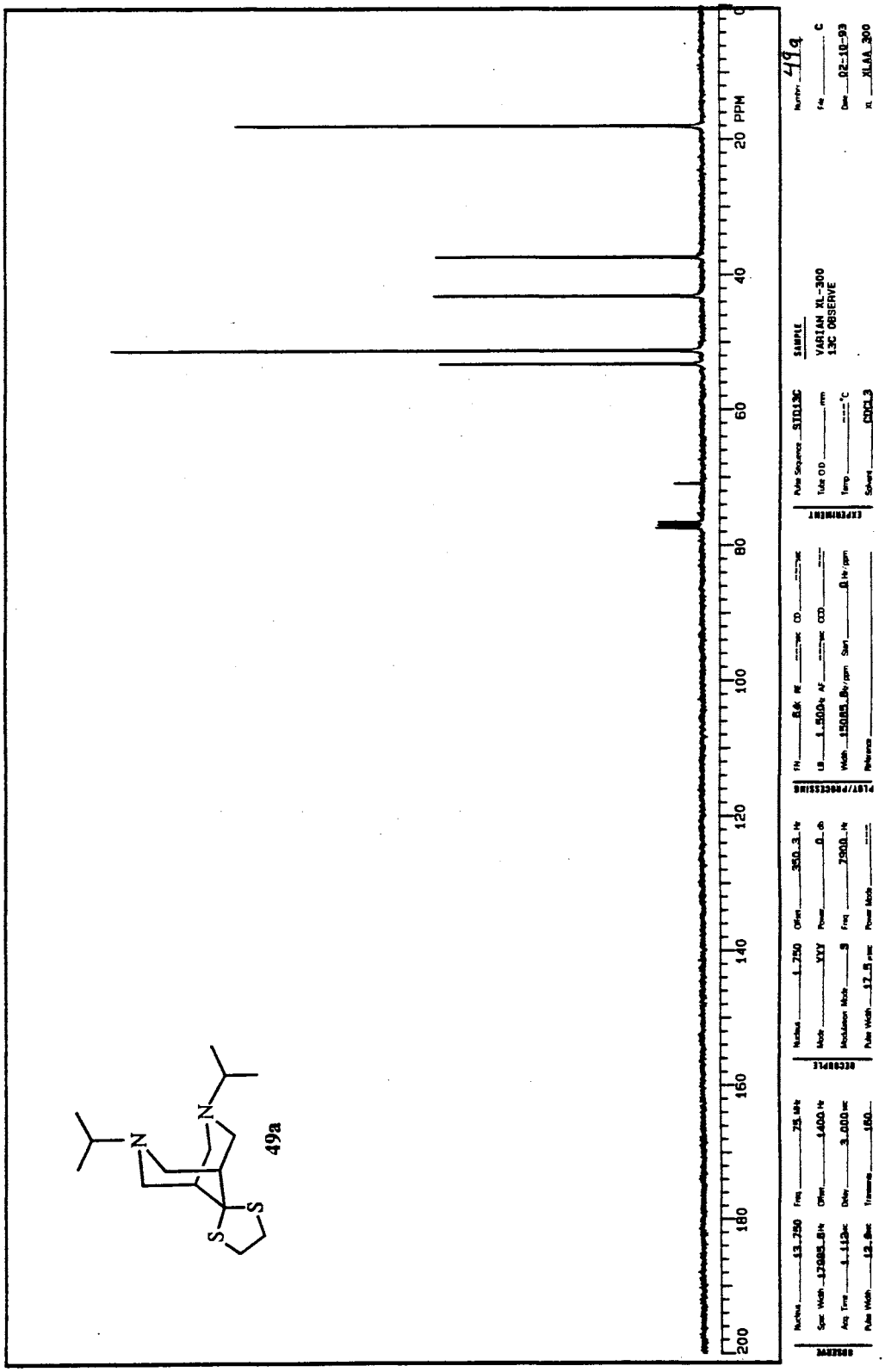
IR Spectrum of **49a**

Plate XLIV



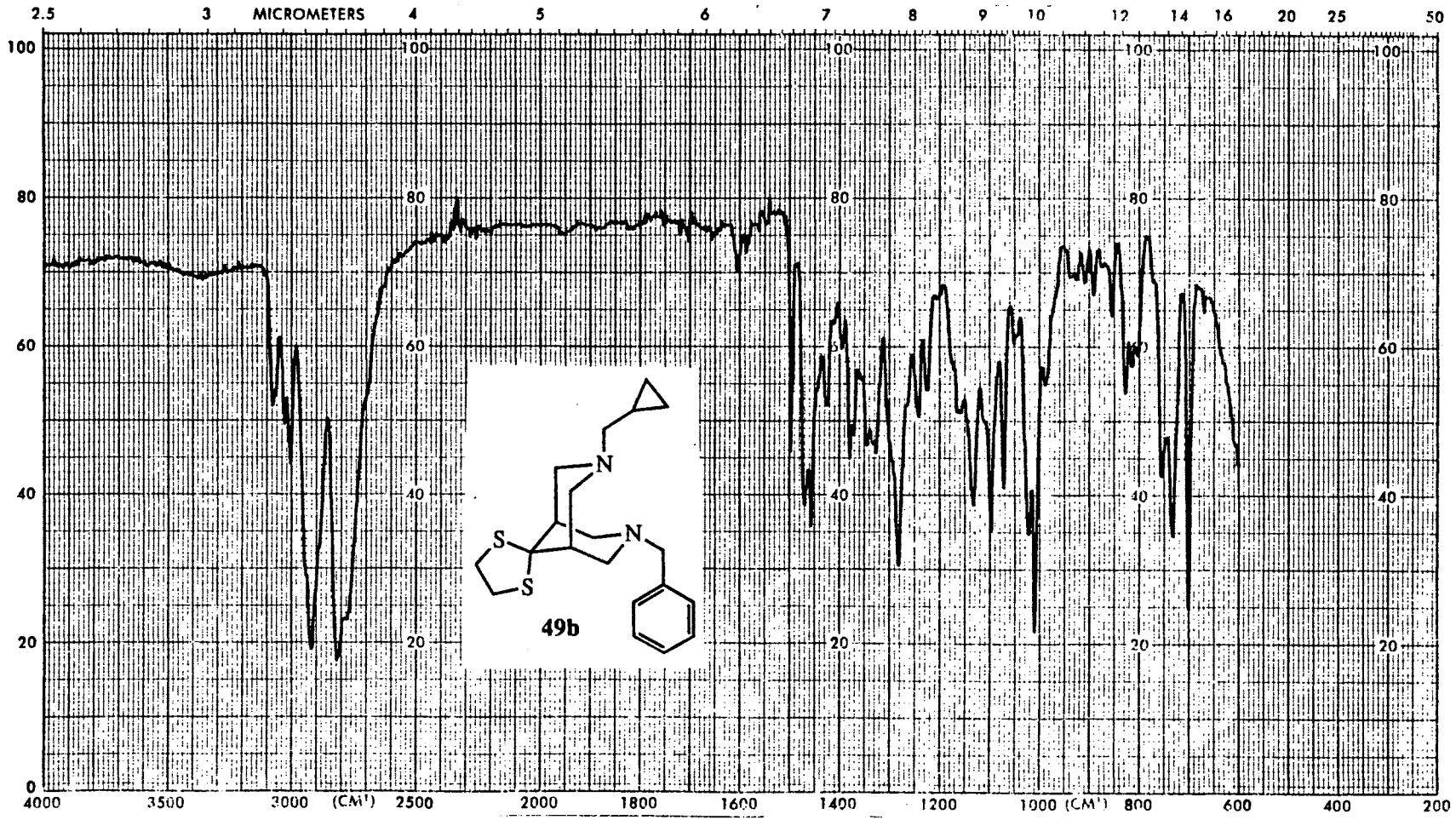
^{1}H NMR Spectrum of **49a**

Plate XLV



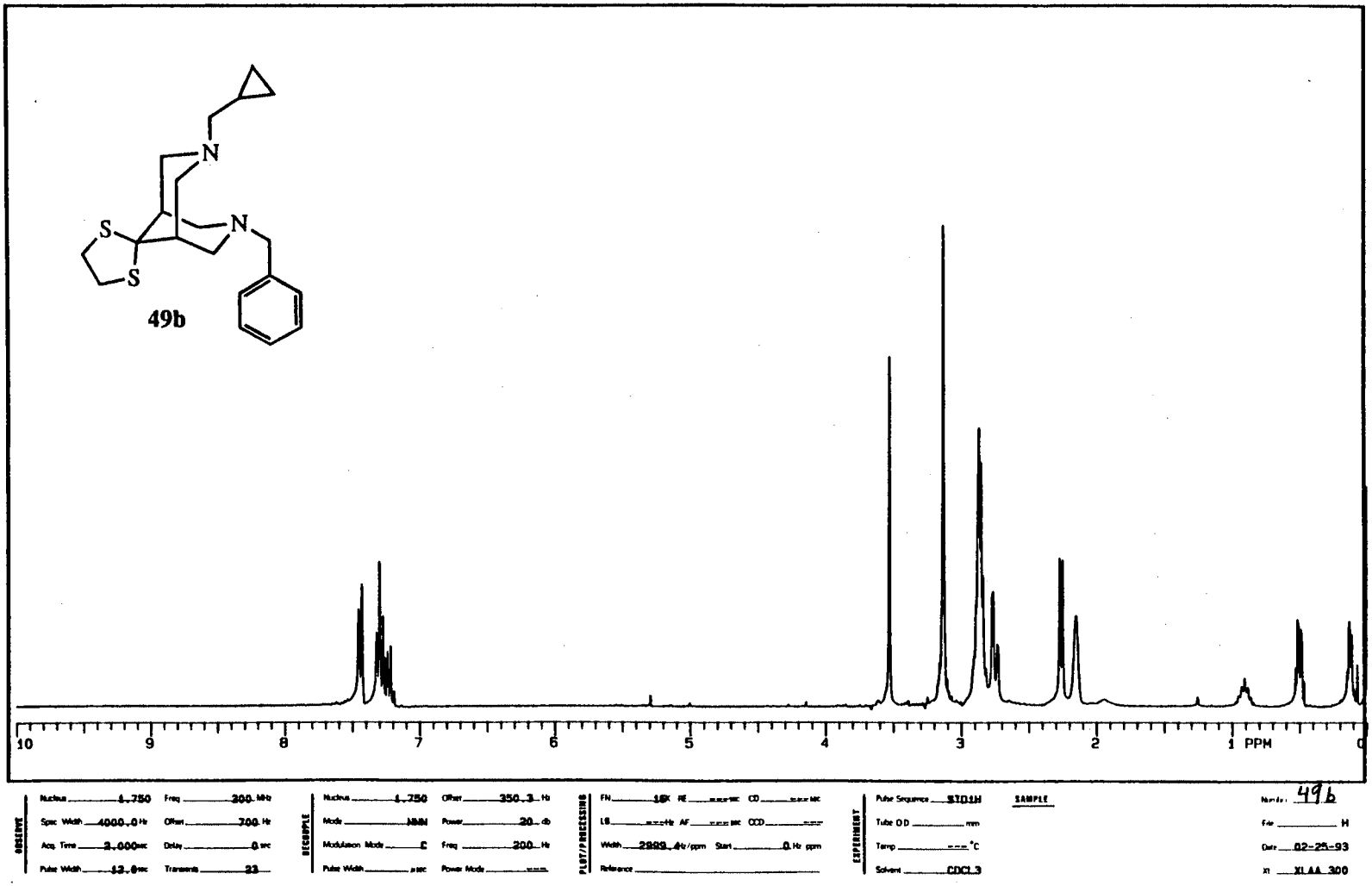
^{13}C NMR Spectrum of **49a**

Plate XLVI



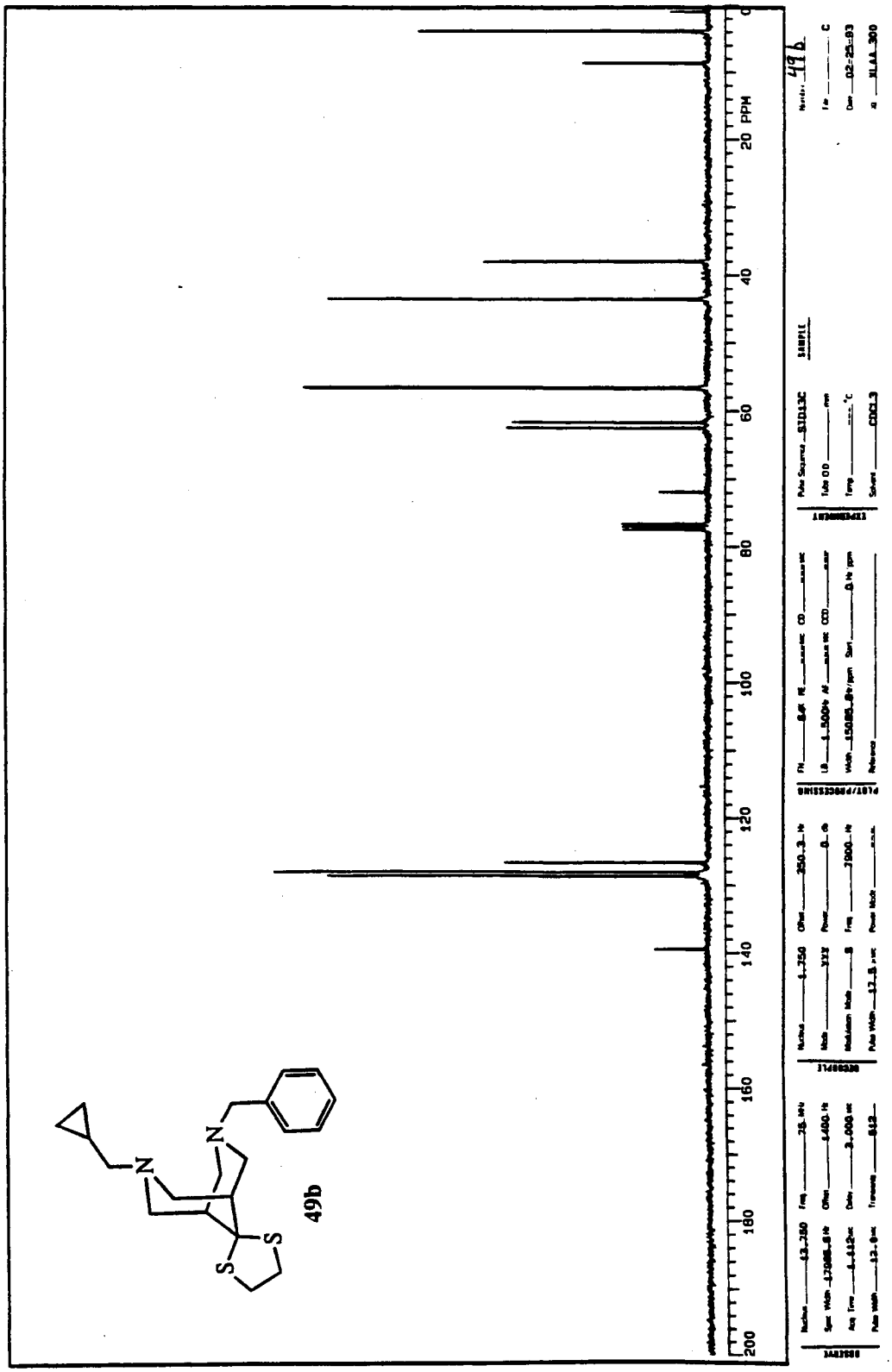
IR Spectrum of **49b**

Plate XLVII



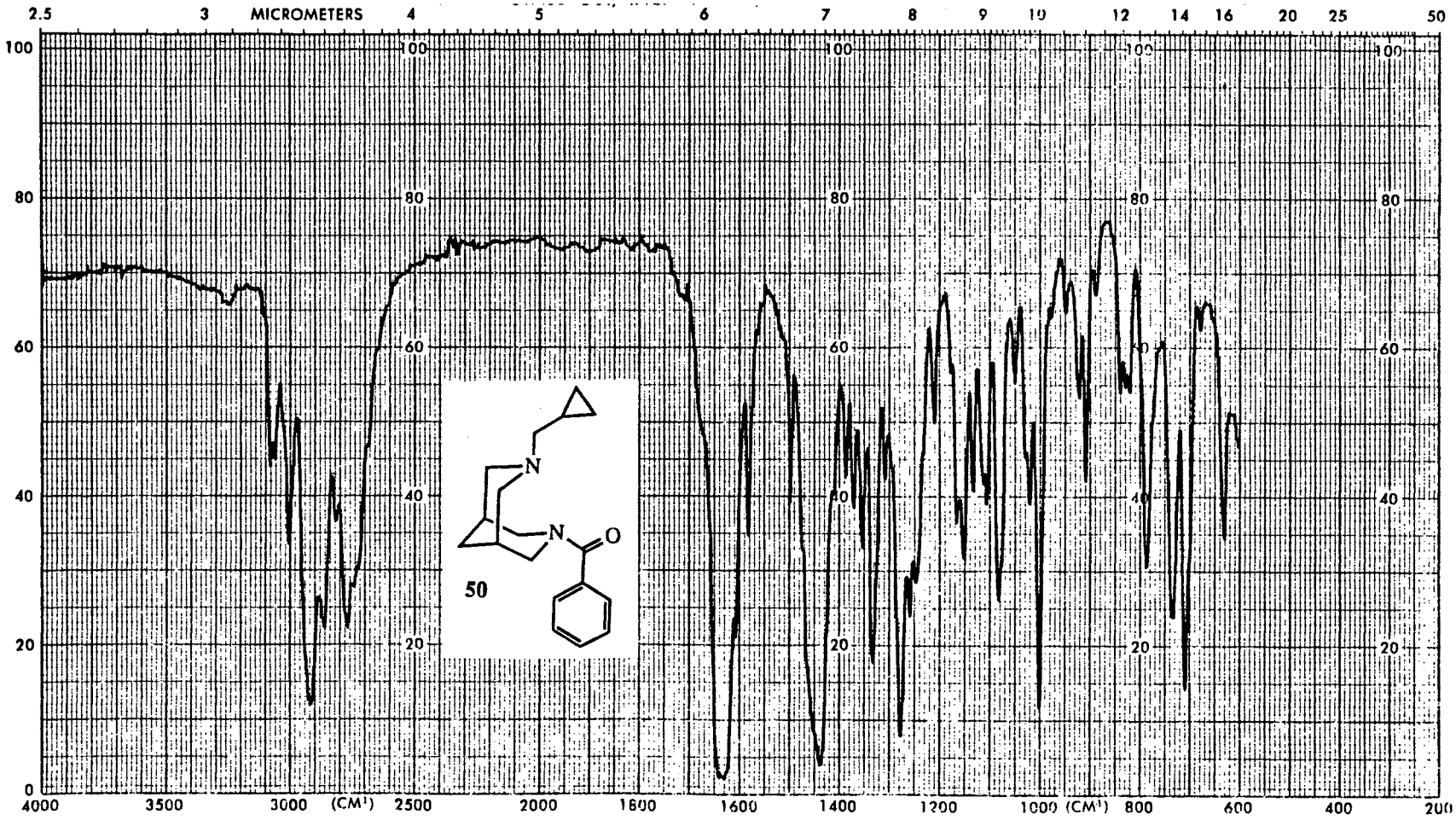
^{1}H NMR Spectrum of **49b**

Plate XLVIII



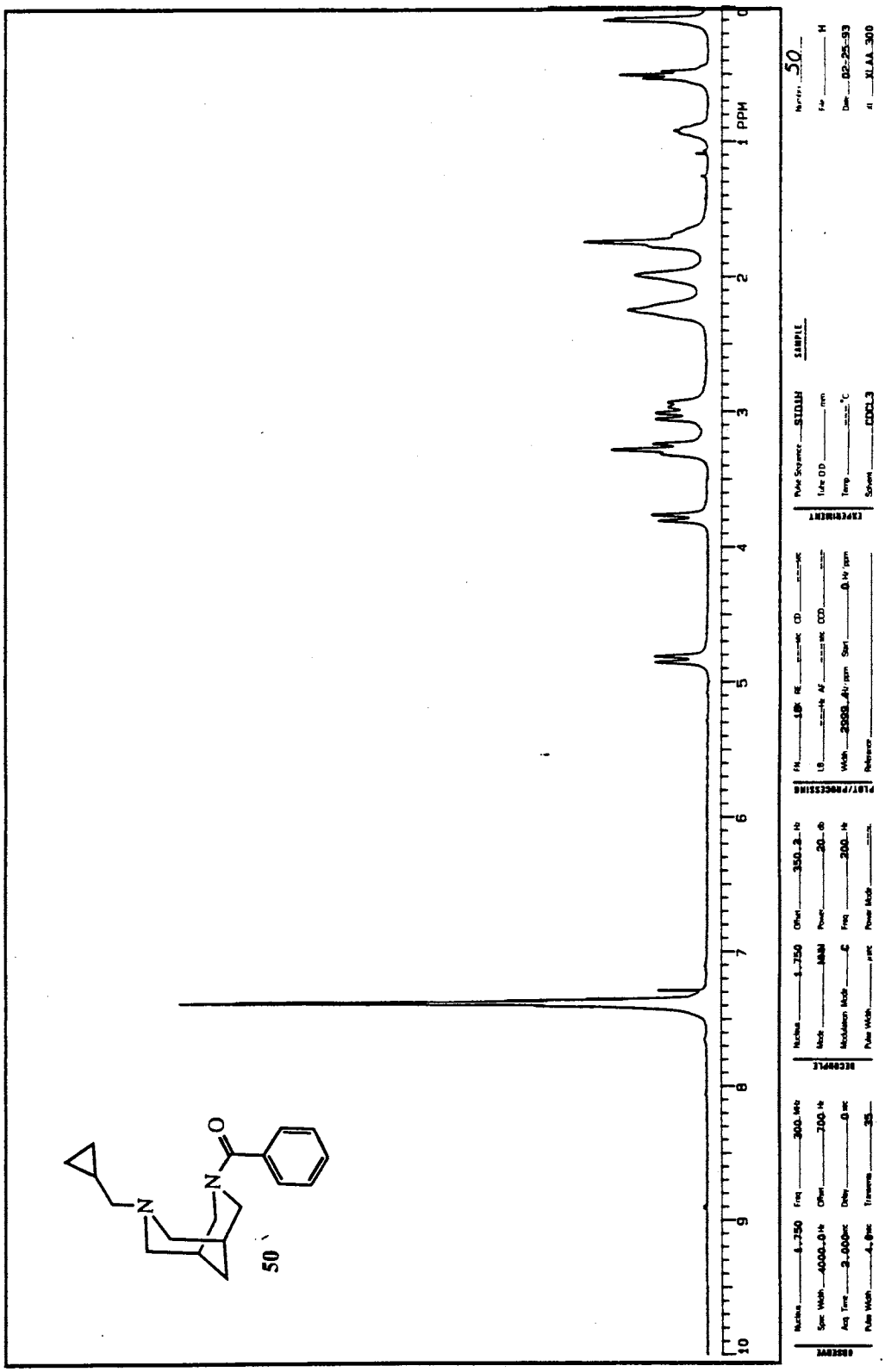
^{13}C NMR Spectrum of **49b**

Plate XLIX



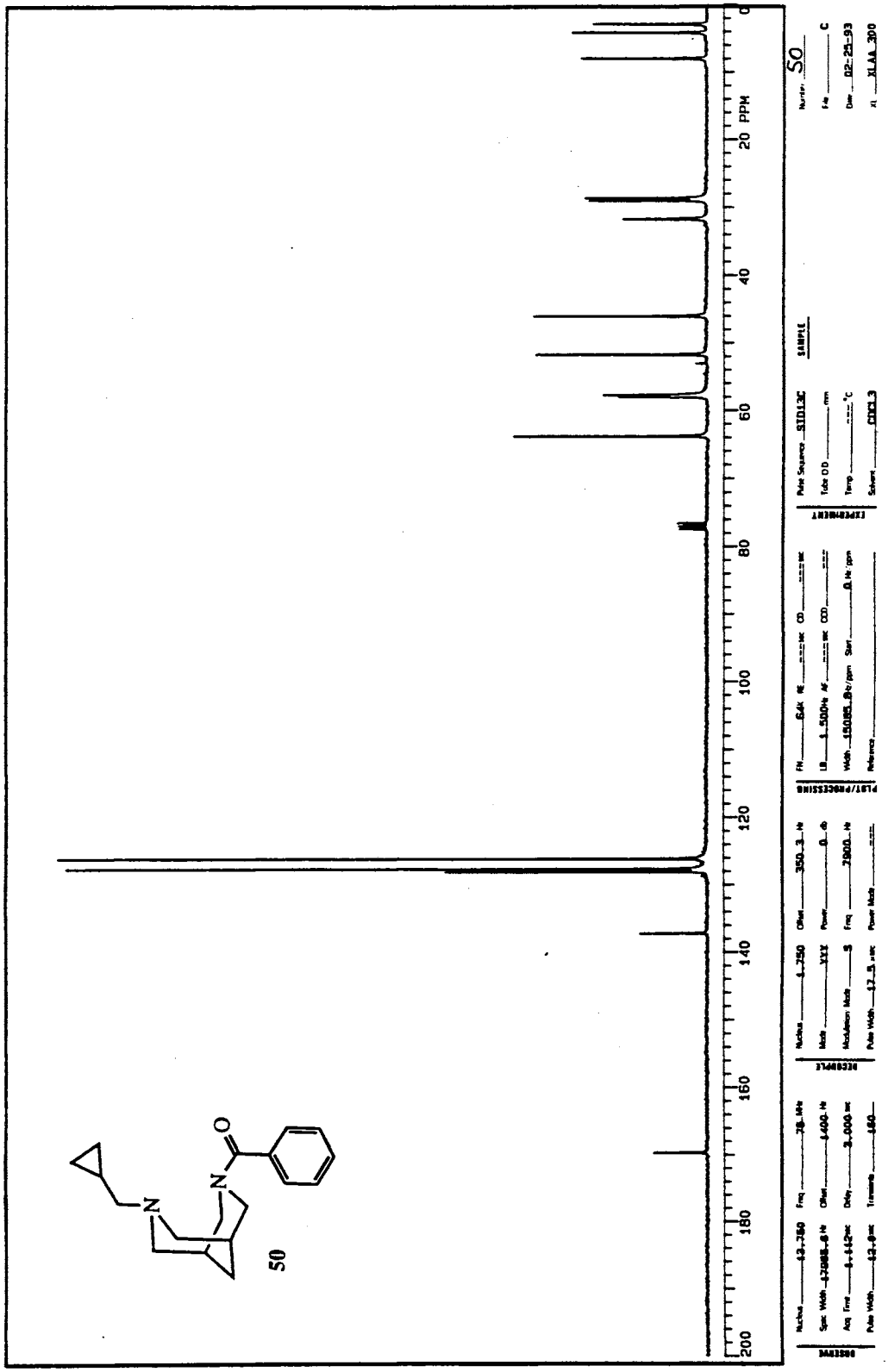
IR Spectrum of **50**

Plate L



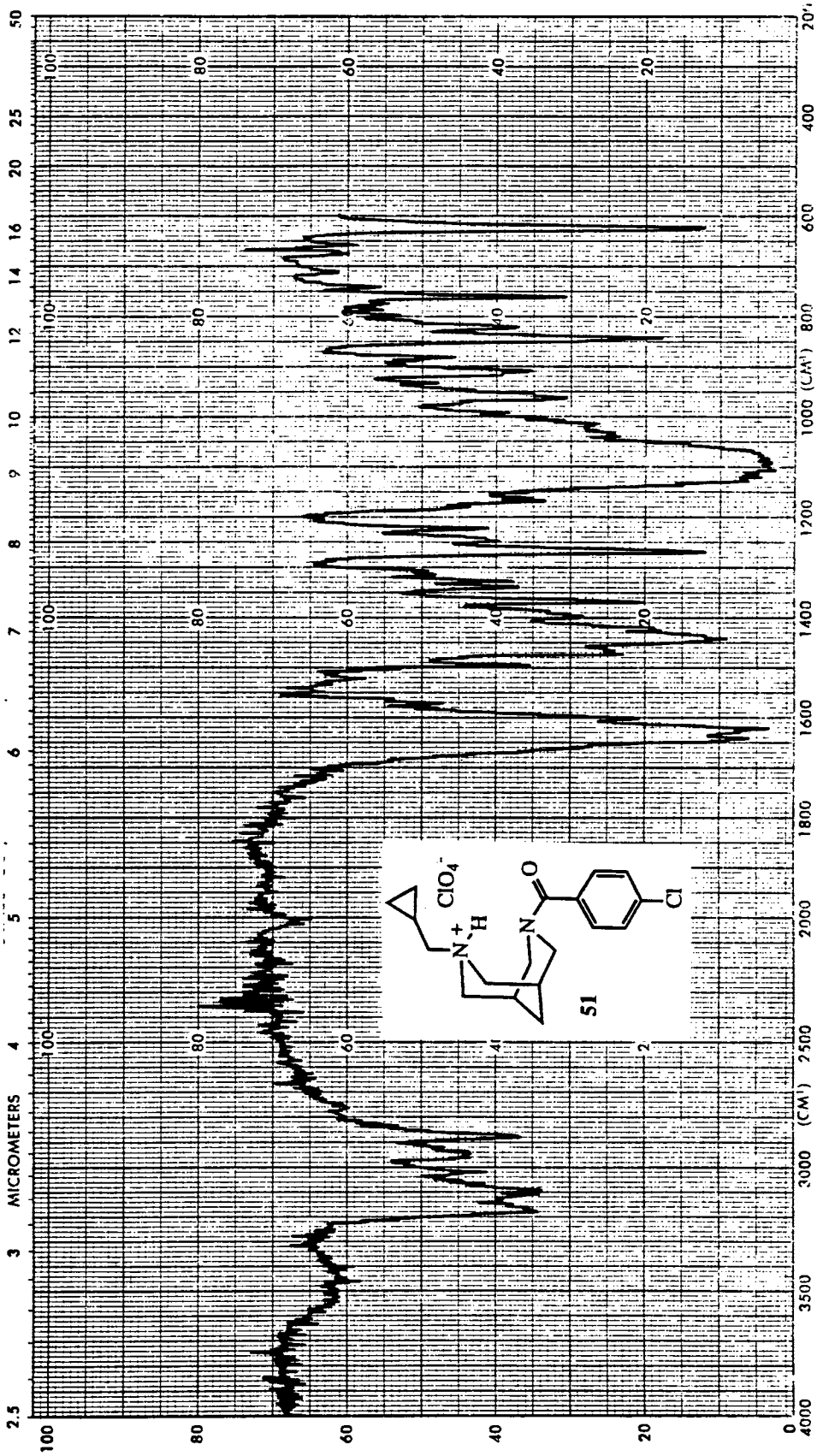
^{1}H NMR Spectrum of **50**

Plate LI



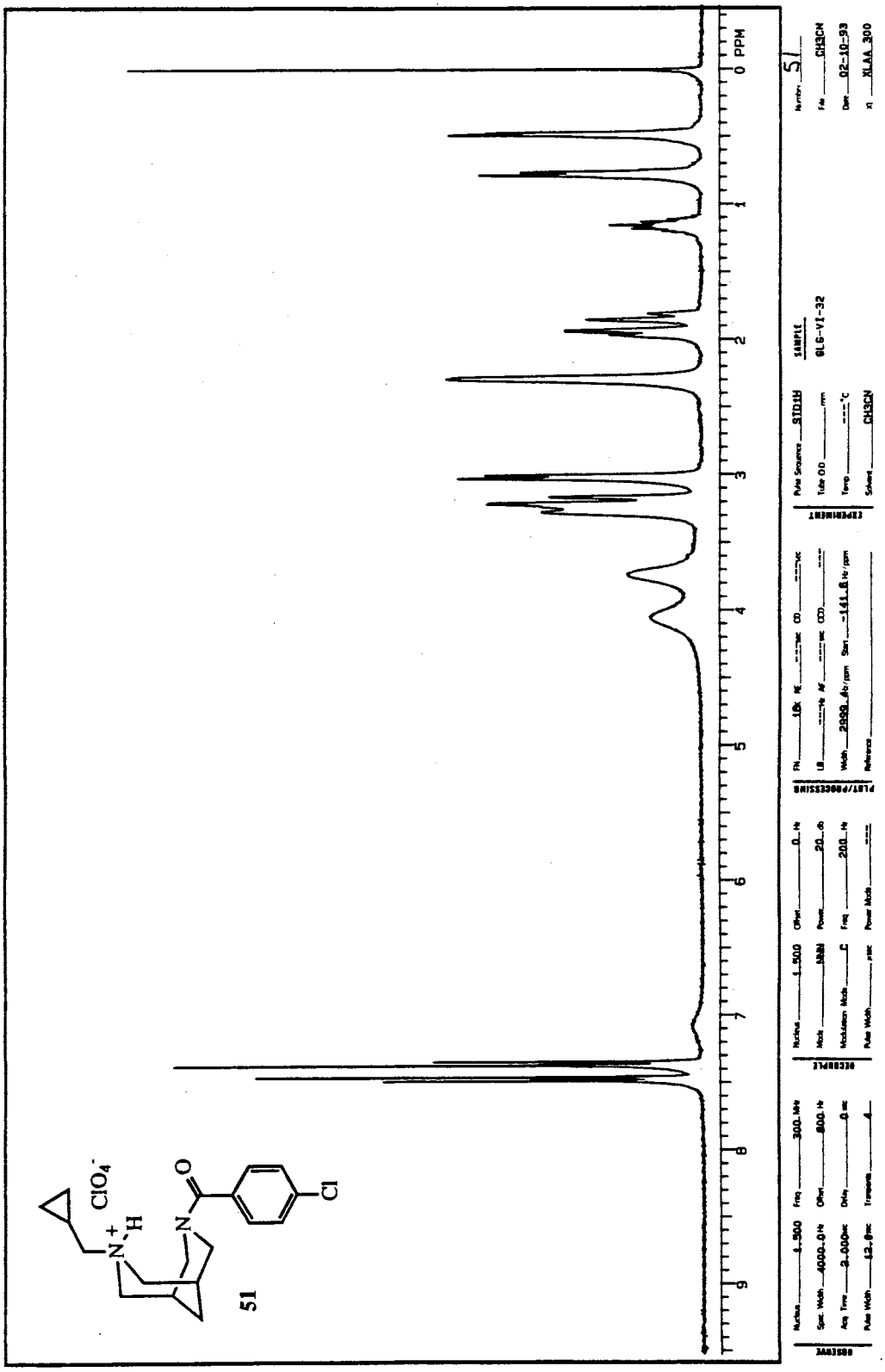
^{13}C NMR Spectrum of **50**

Plate LII



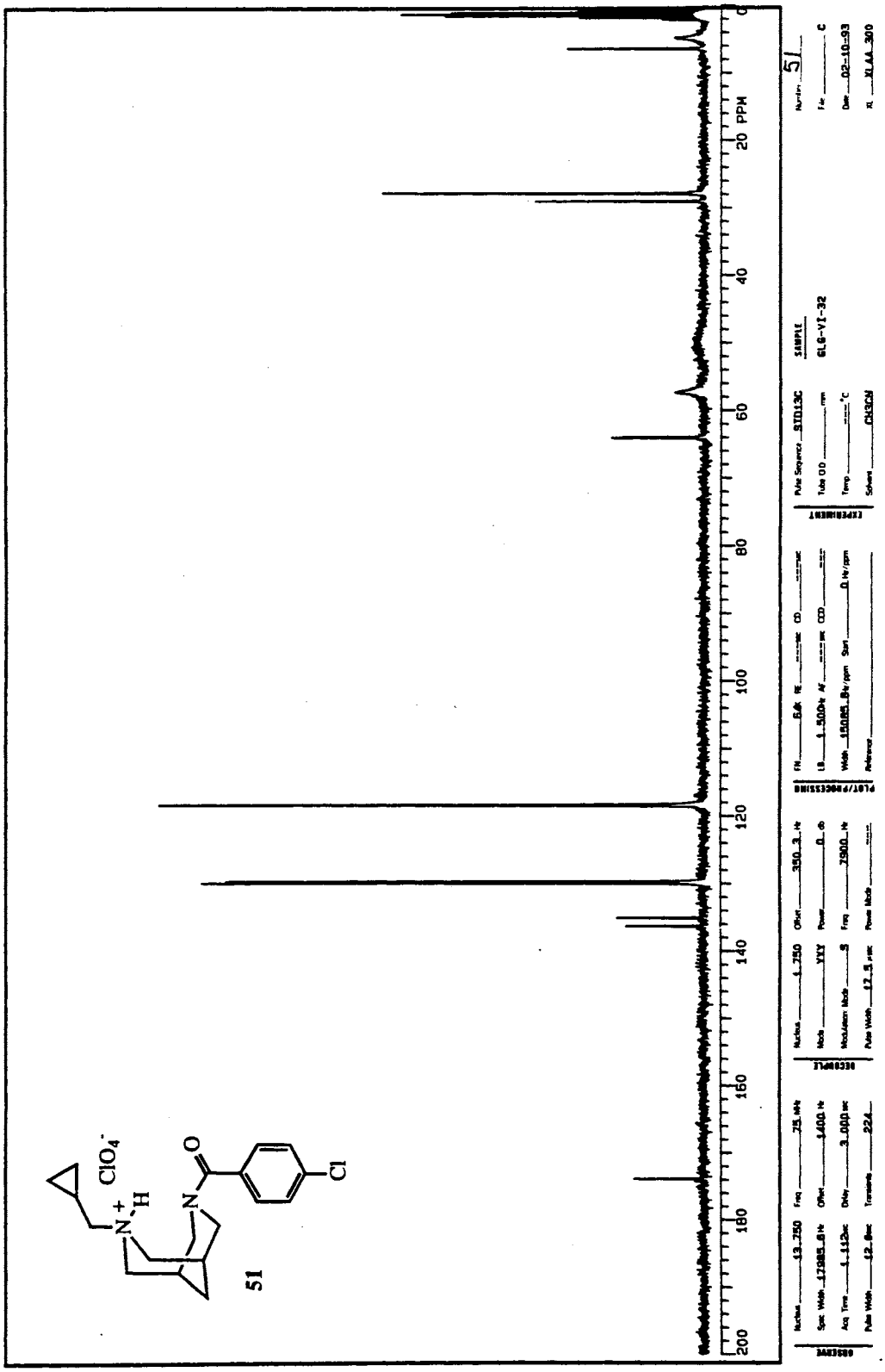
IR Spectrum of **51**

Plate LIII

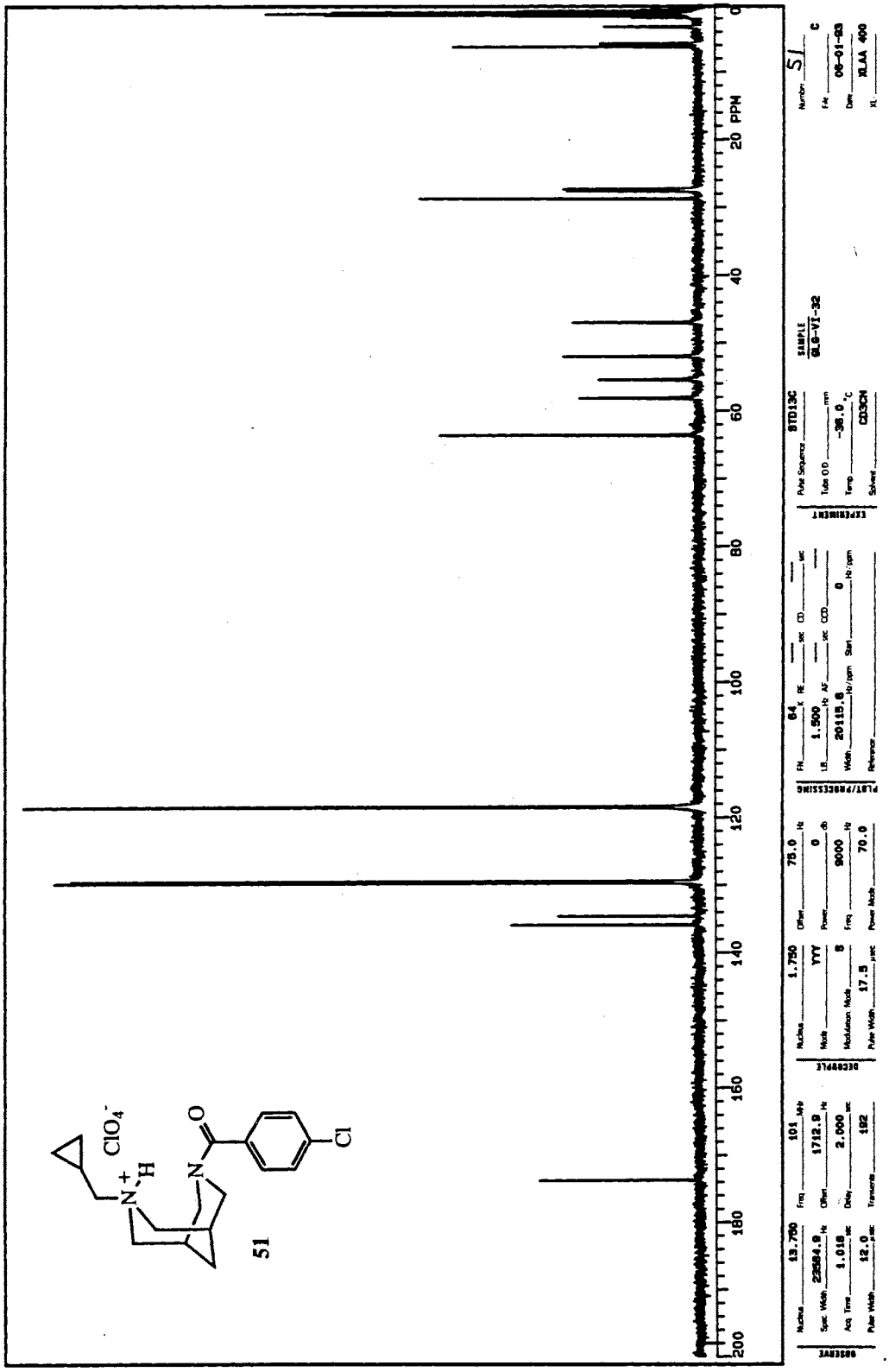


^{1}H NMR Spectrum of **51**

Plate LIV

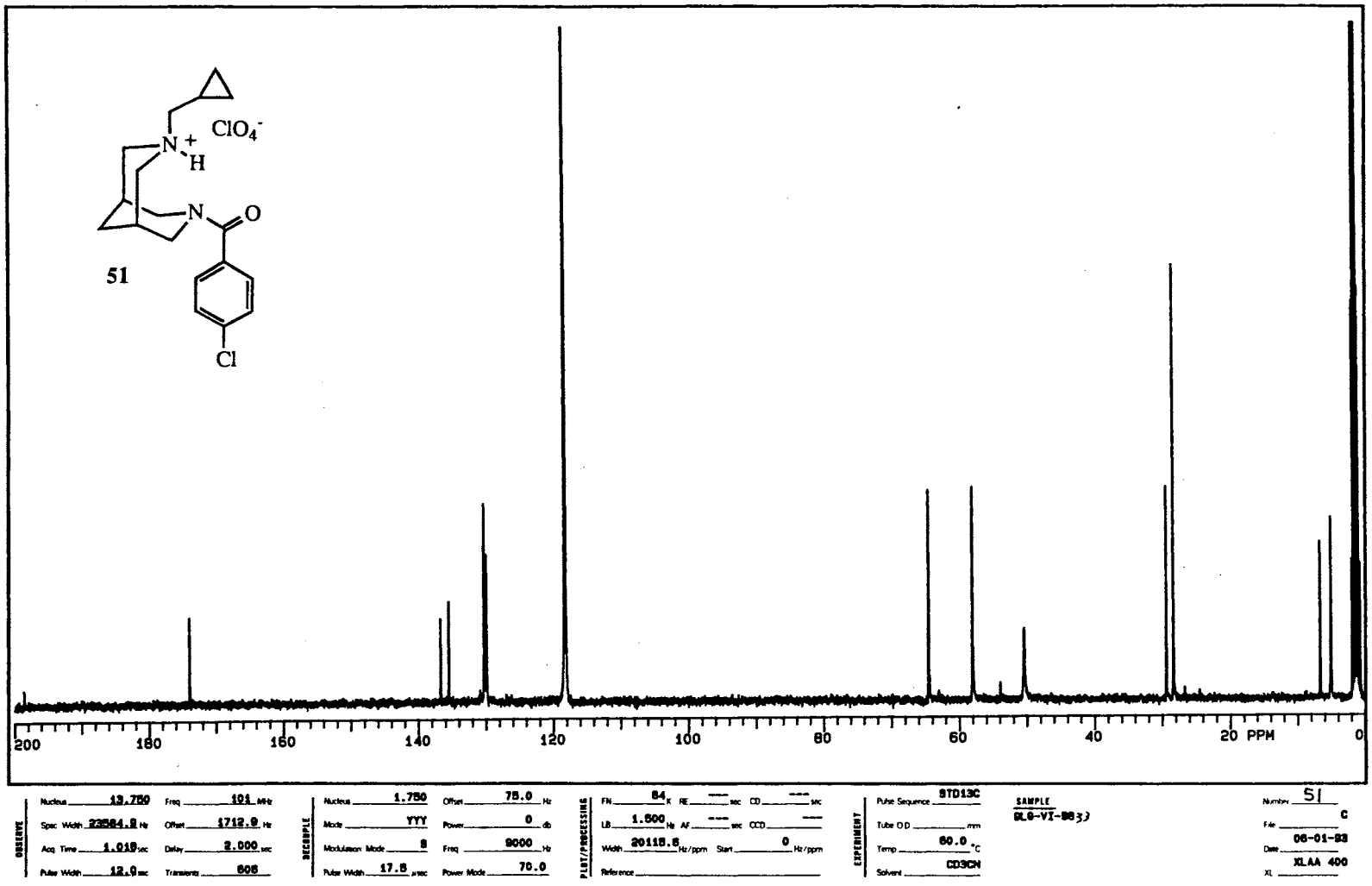


^{13}C NMR Spectrum (RT) of **51**



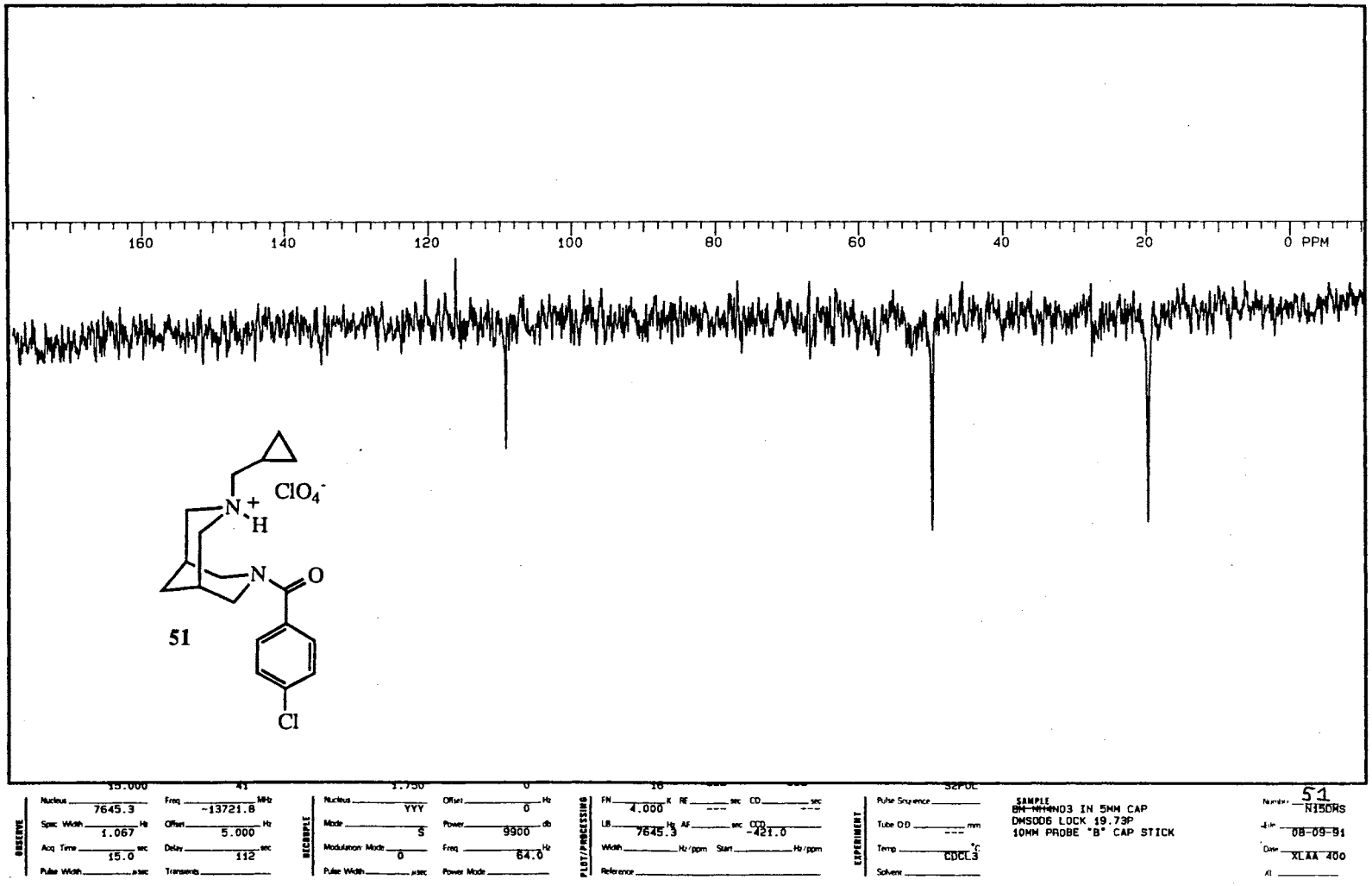
^{13}C NMR Spectrum (-35°C) of **51**

Plate LVI



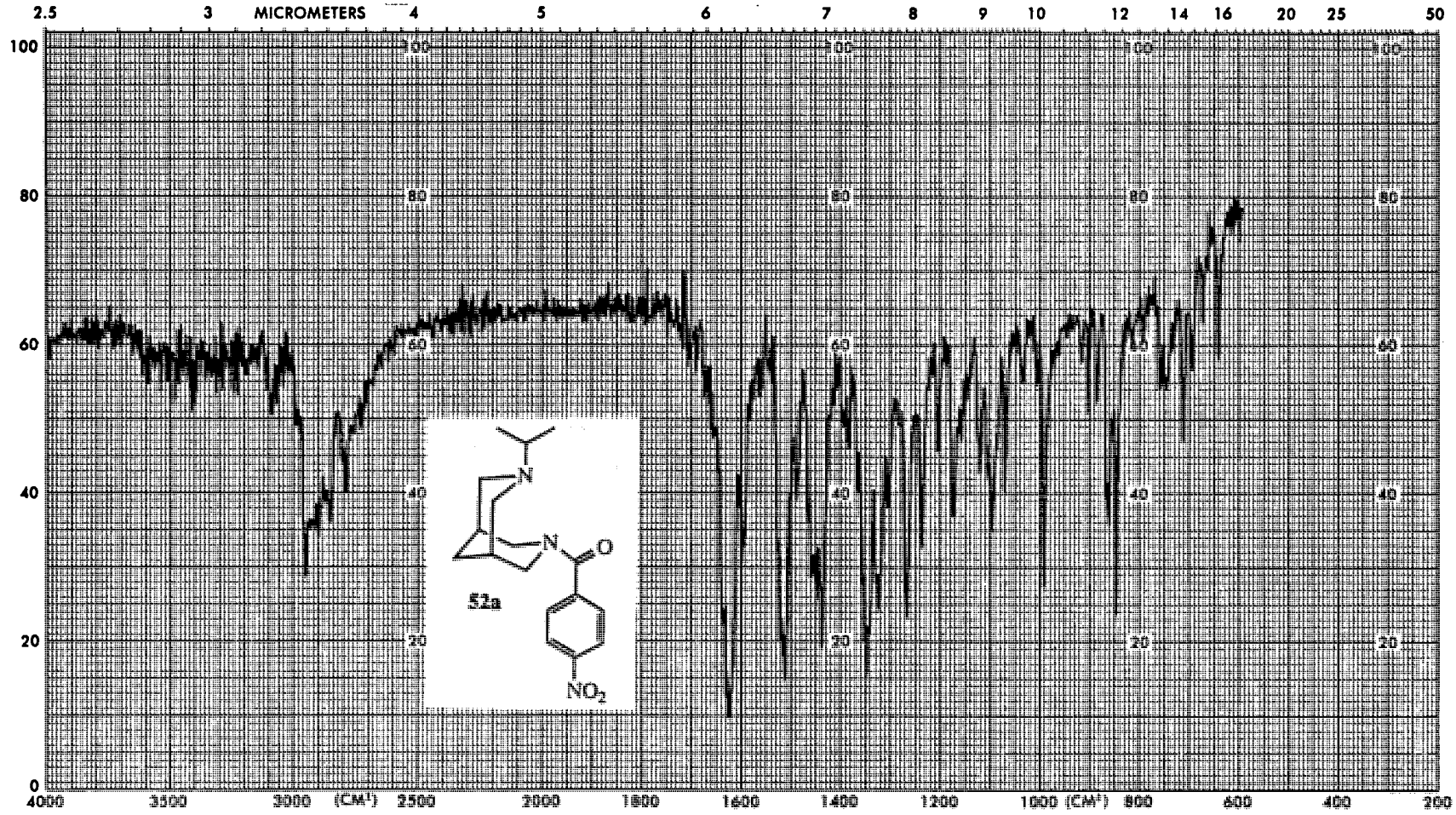
^{13}C NMR Spectrum (60°C) of **51**

Plate LVII



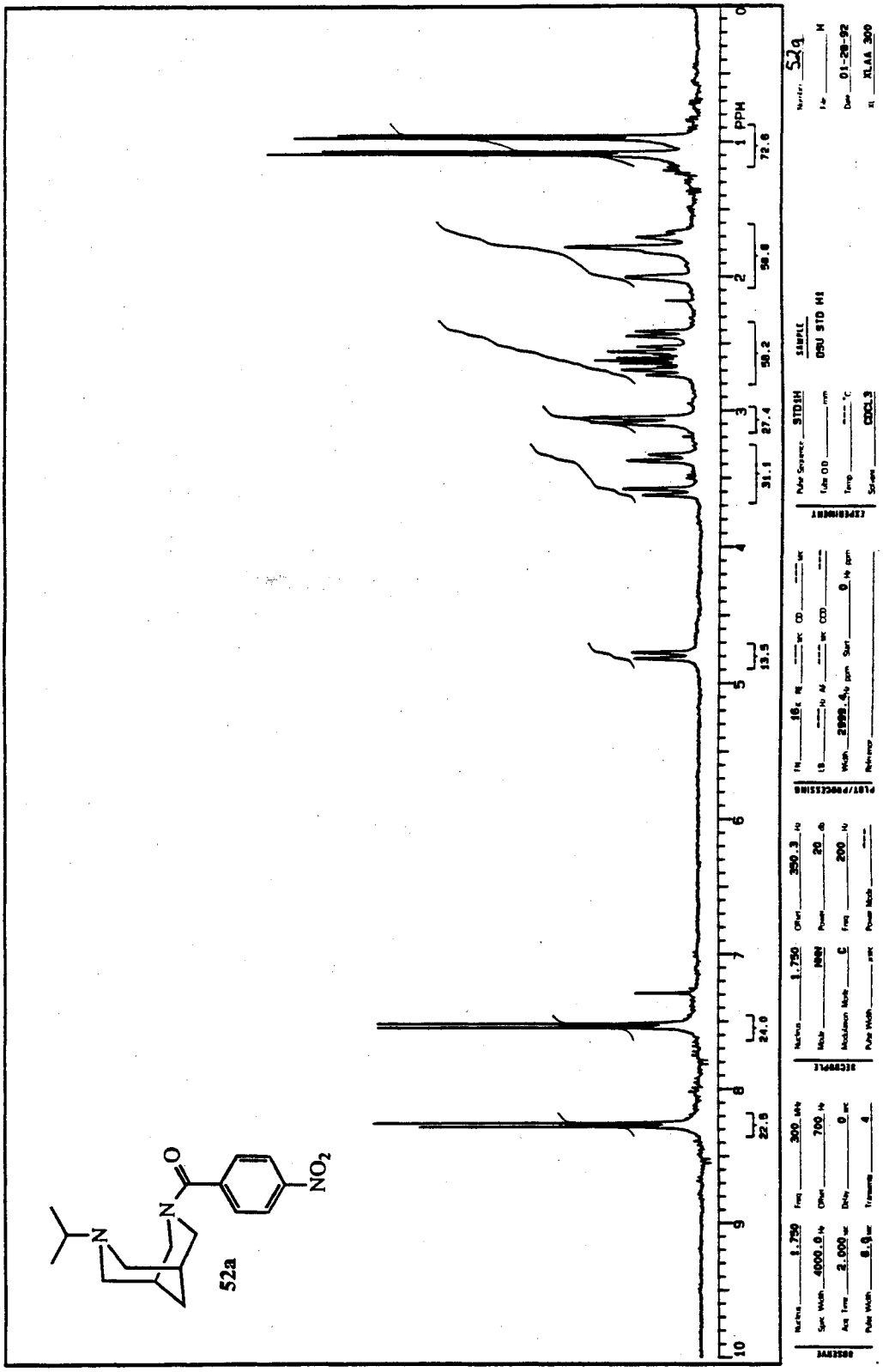
^{15}N NMR Spectrum of **51**

Plate LVIII



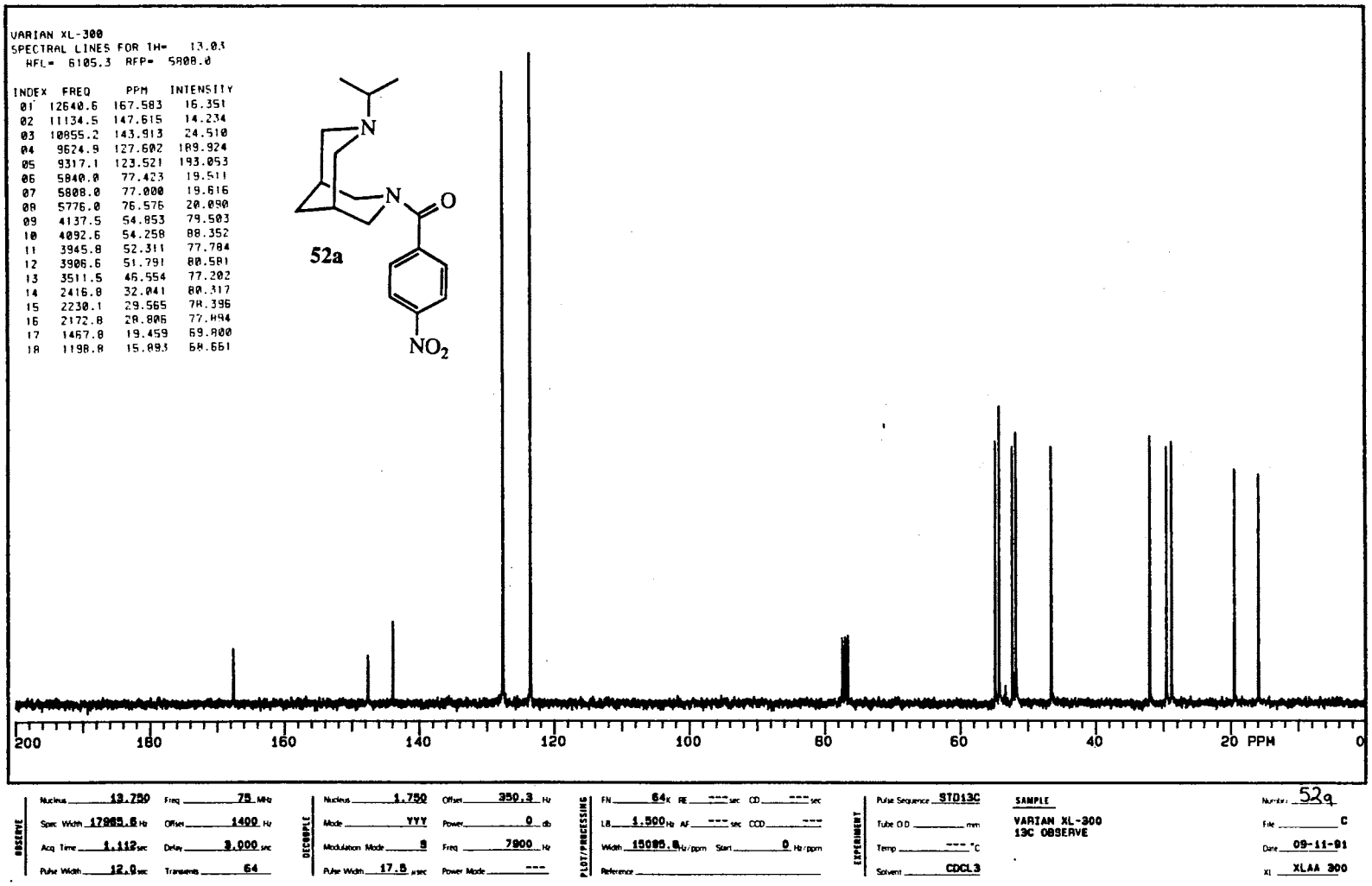
IR Spectrum of **52a**

Plate LIX



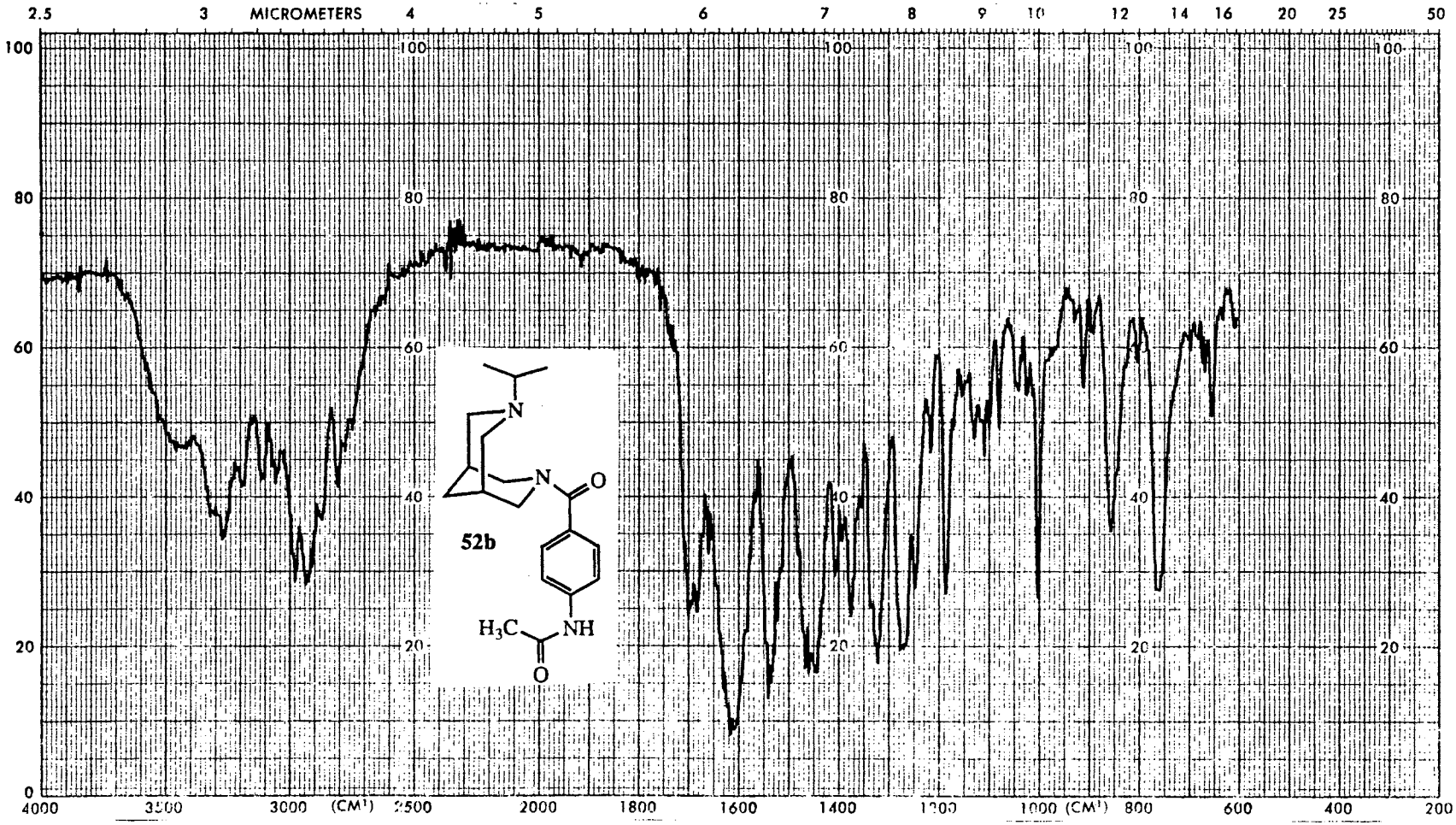
^{1}H NMR Spectrum of **52a**

Plate LX



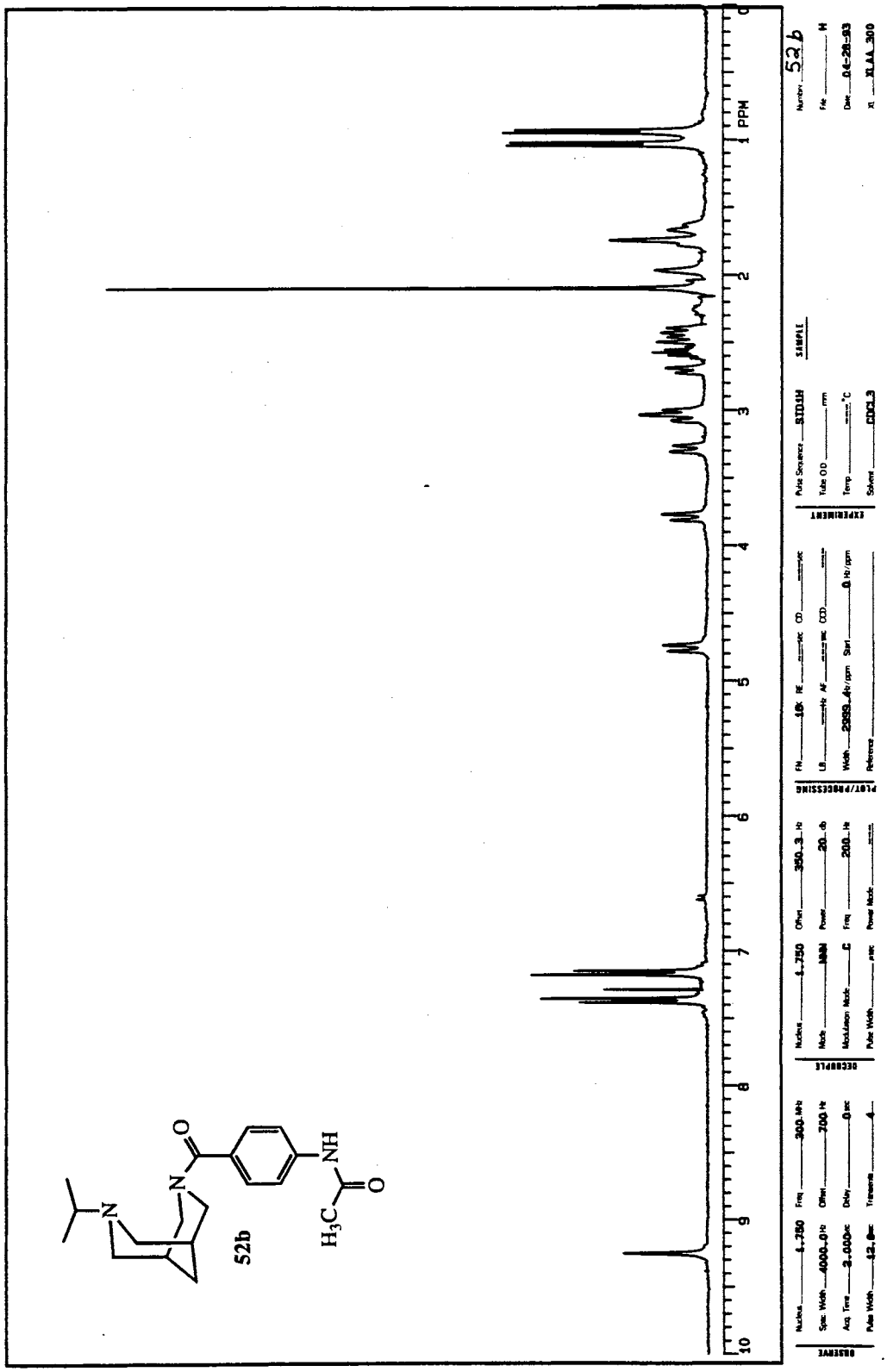
^{13}C NMR Spectrum of **52a**

Plate LXI



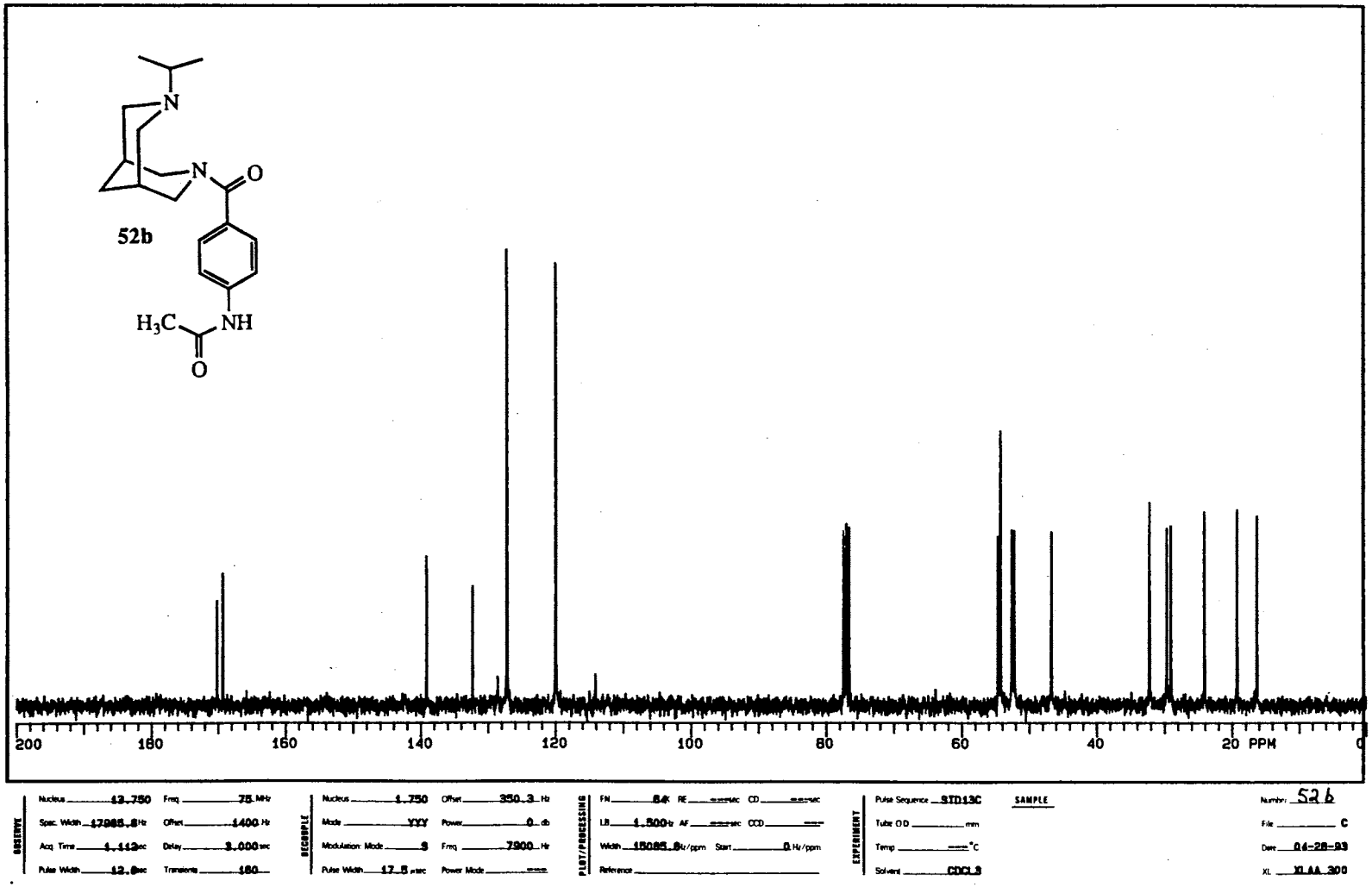
IR Spectrum of **52b**

Plate LXII



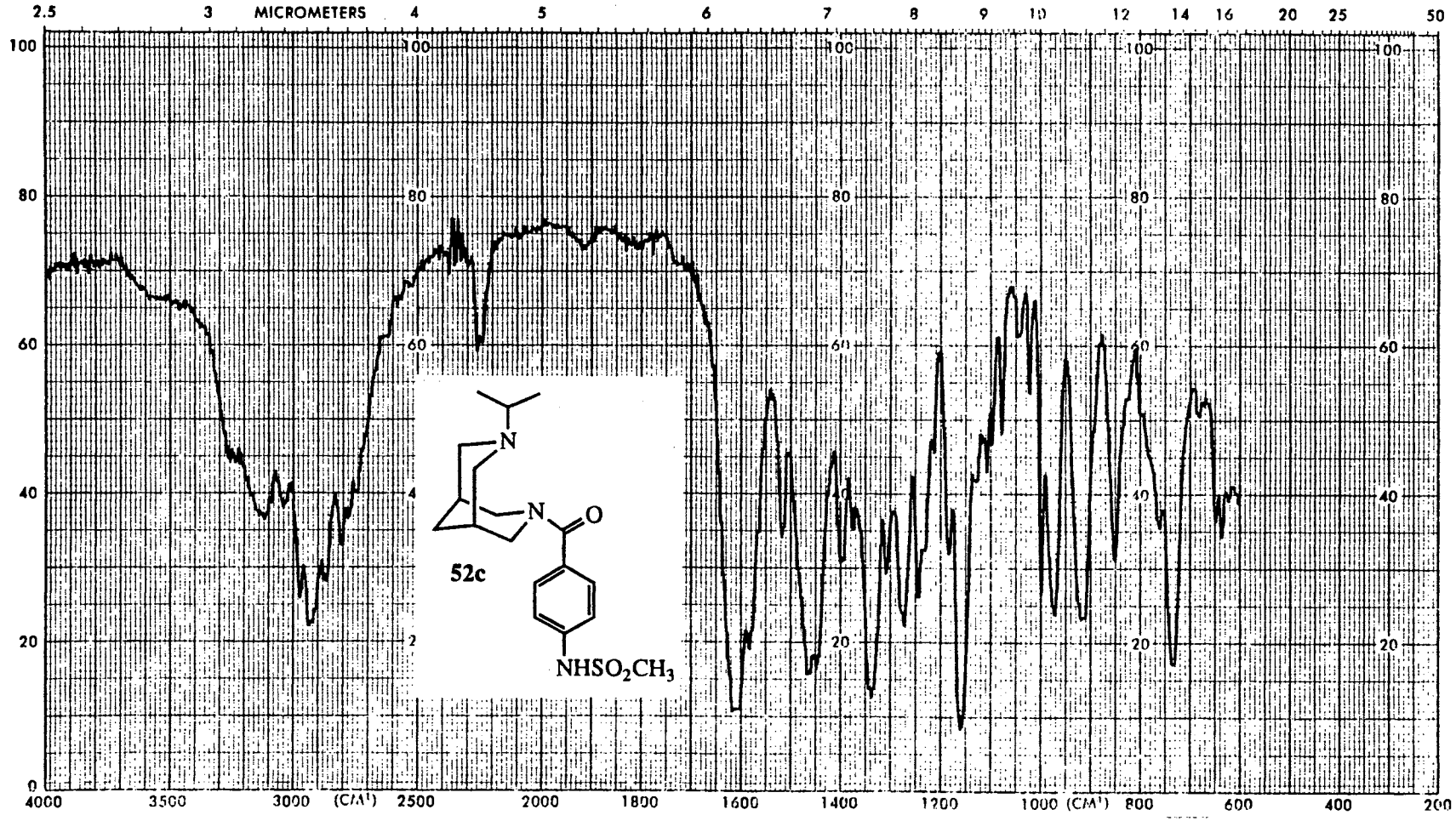
^{1}H NMR Spectrum of **52b**

Plate LXIII



^{13}C NMR Spectrum of **52b**

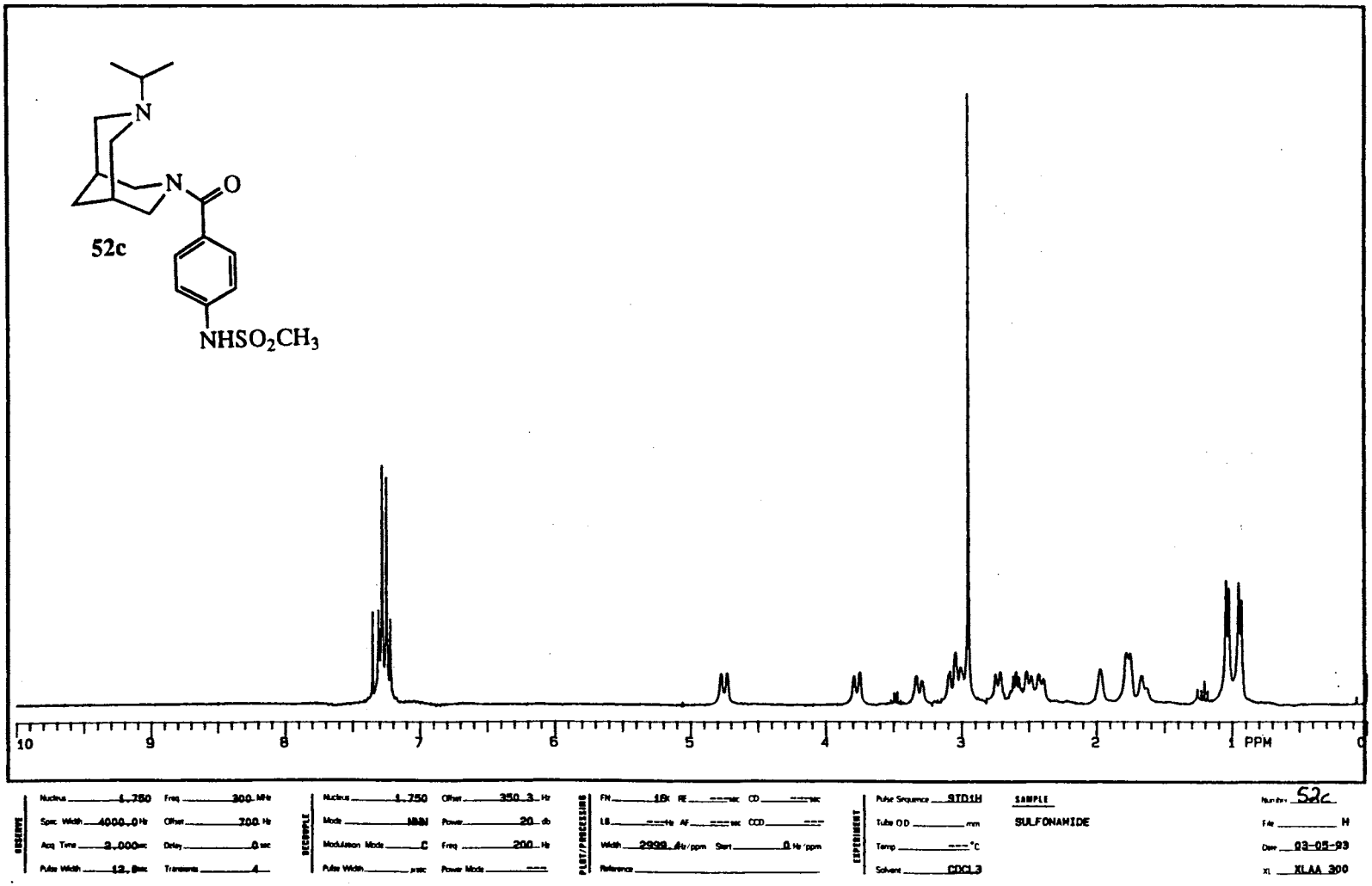
Plate LXIV



52c

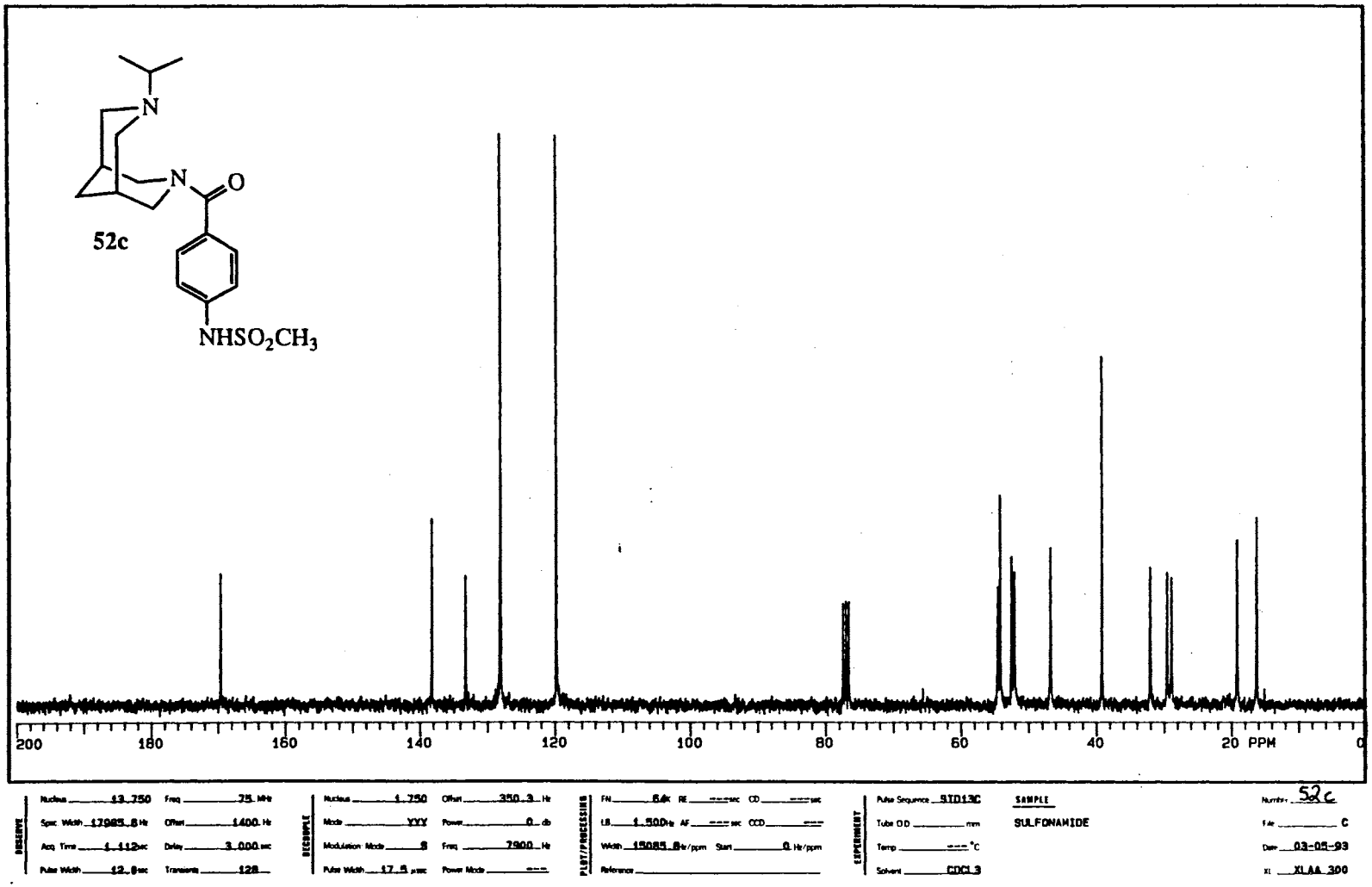
IR Spectrum of **52c**

Plate LXV



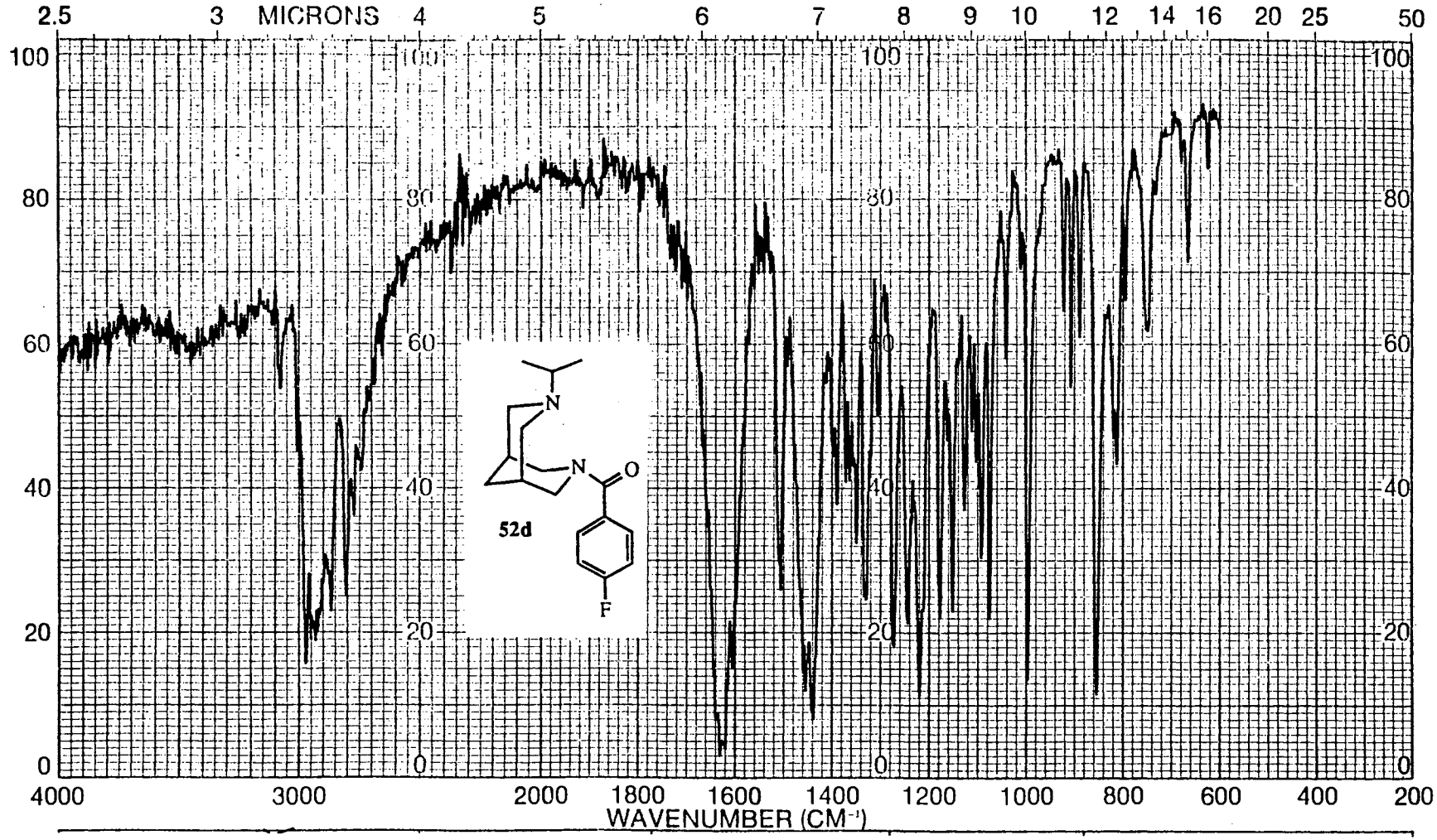
^{1}H NMR Spectrum of **52c**

Plate LXVI



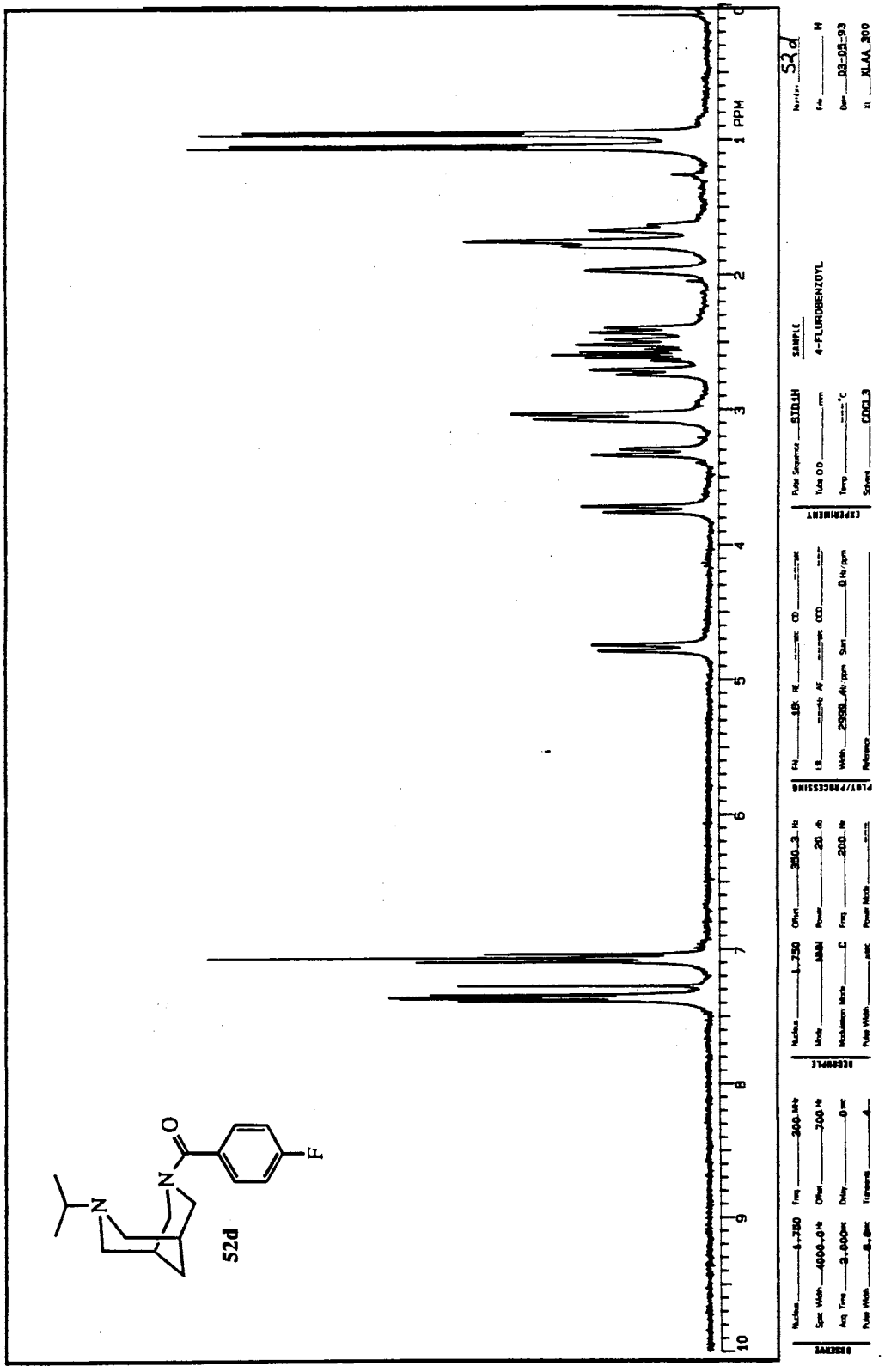
^{13}C NMR Spectrum of **52c**

Plate LXVII



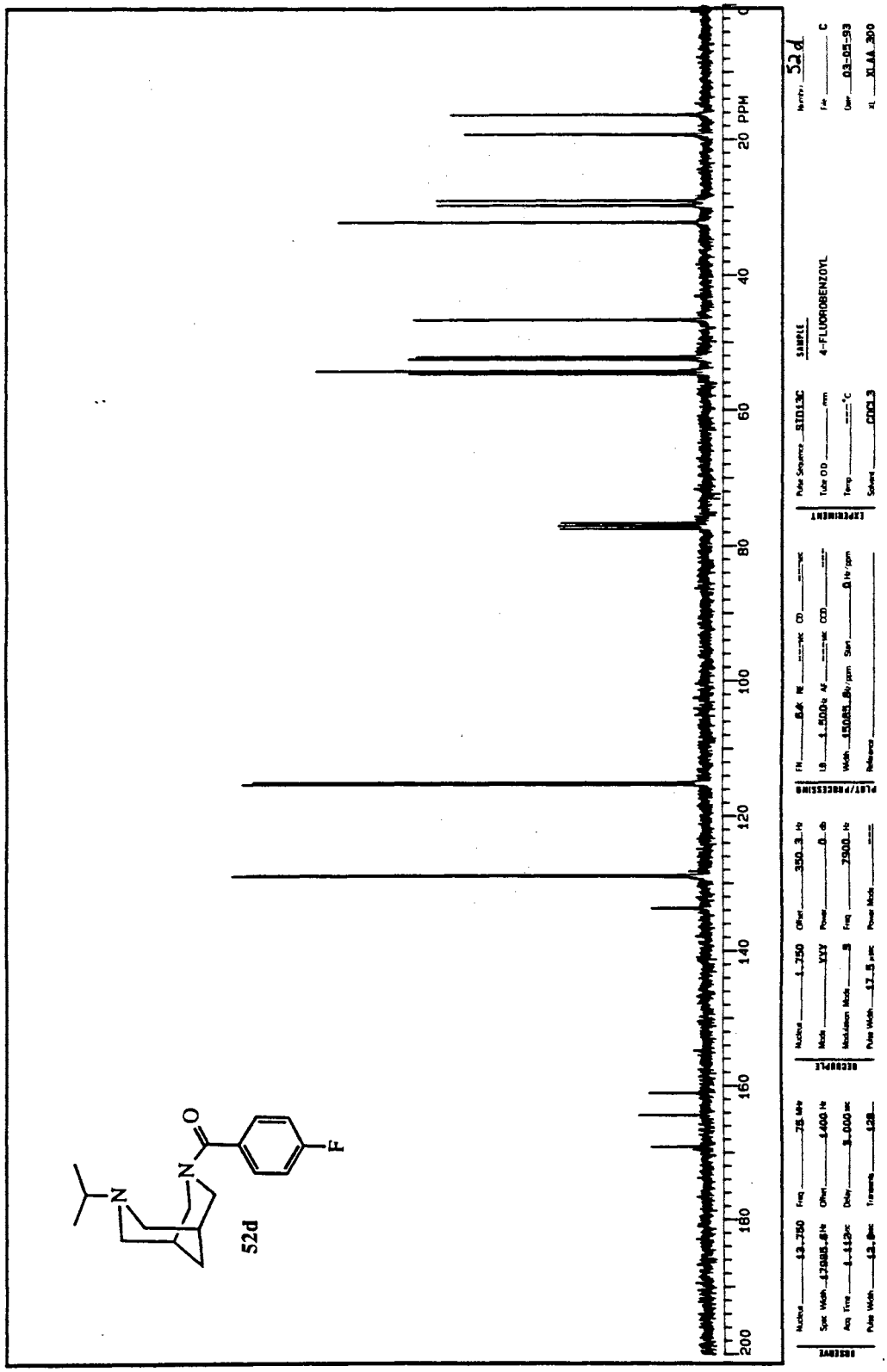
IR Spectrum of **52d**

Plate LXVIII



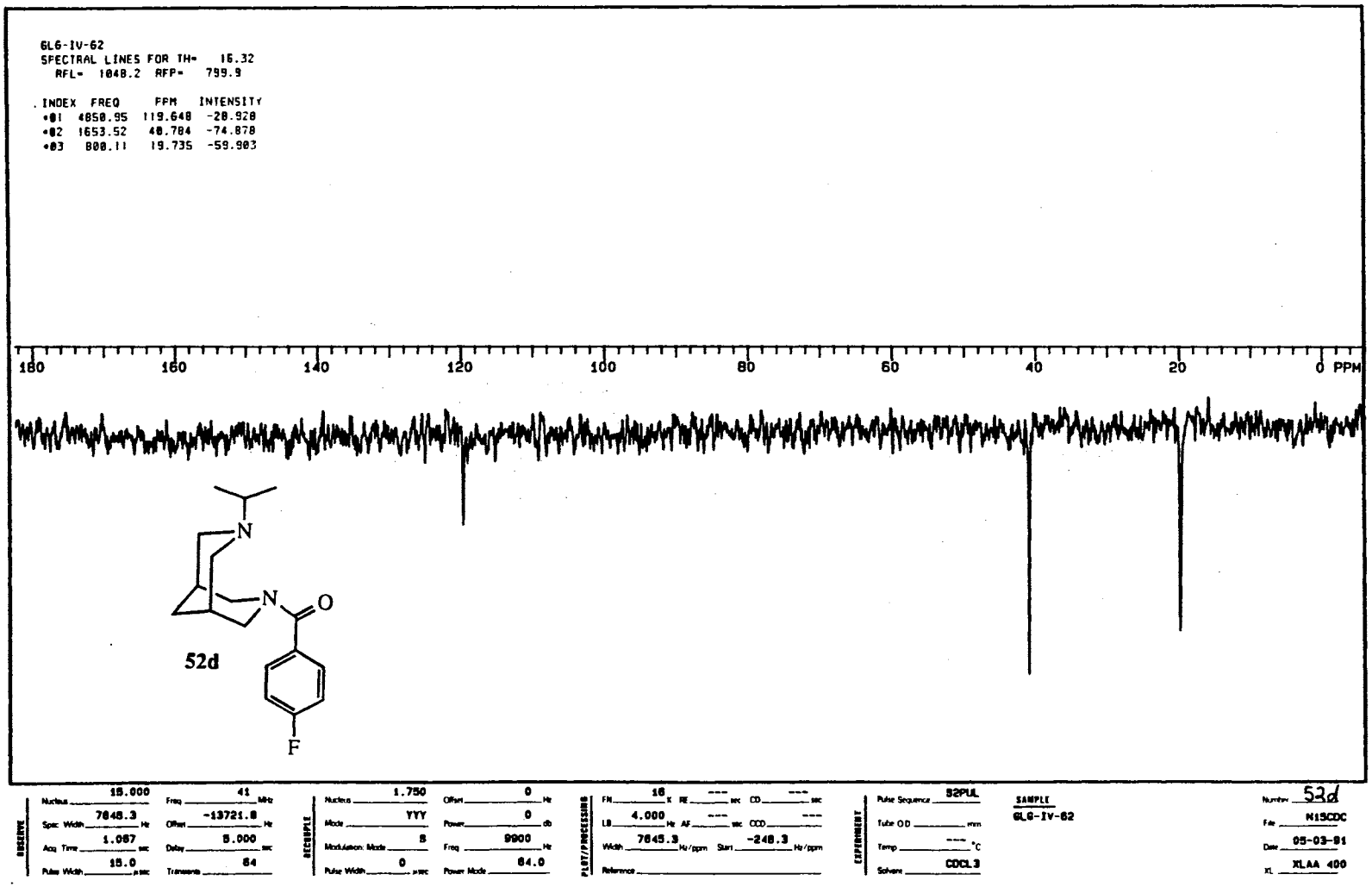
^{1}H NMR Spectrum of **52d**

Plate LXIX



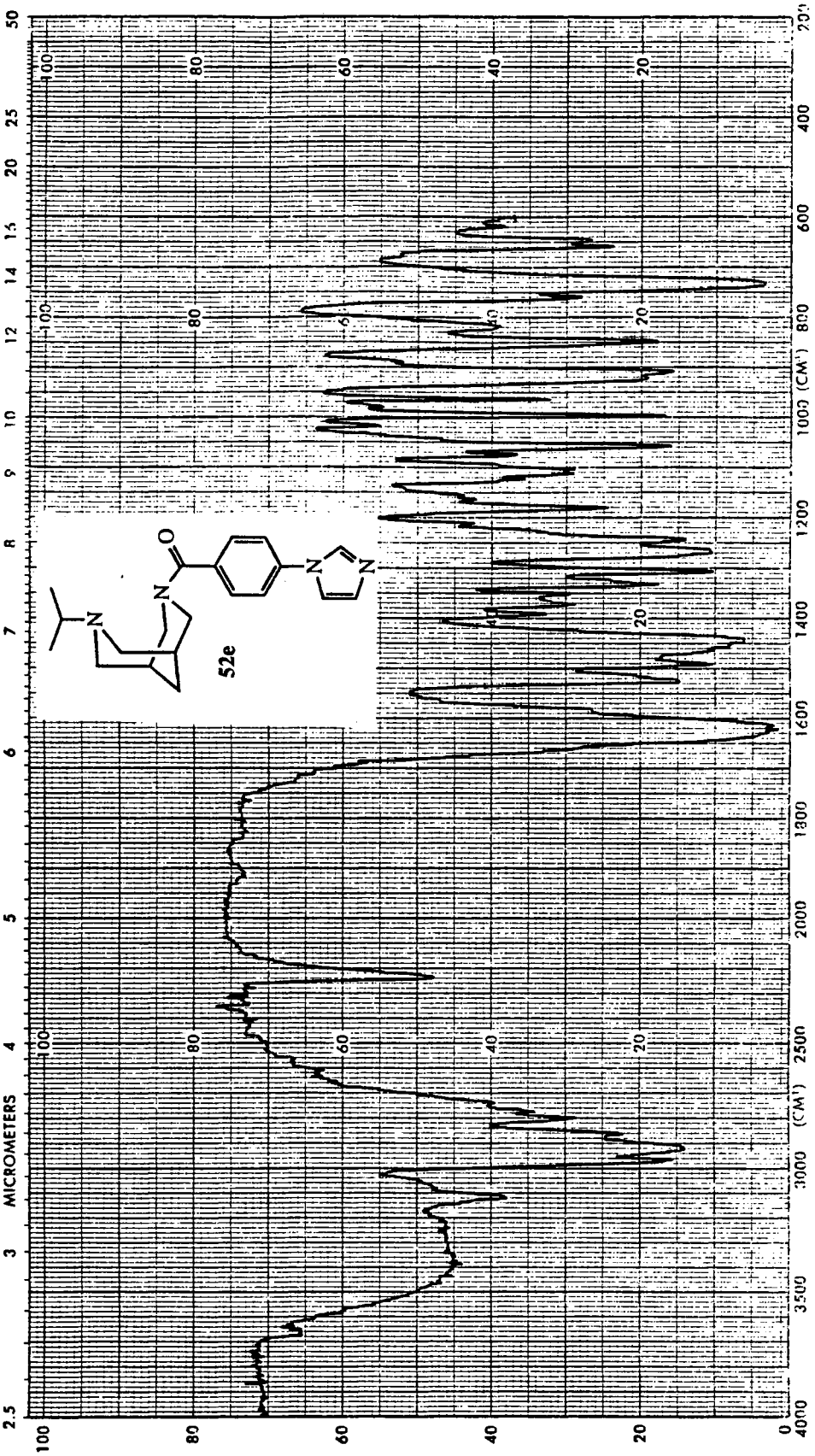
^{13}C NMR Spectrum of **52d**

Plate LXX



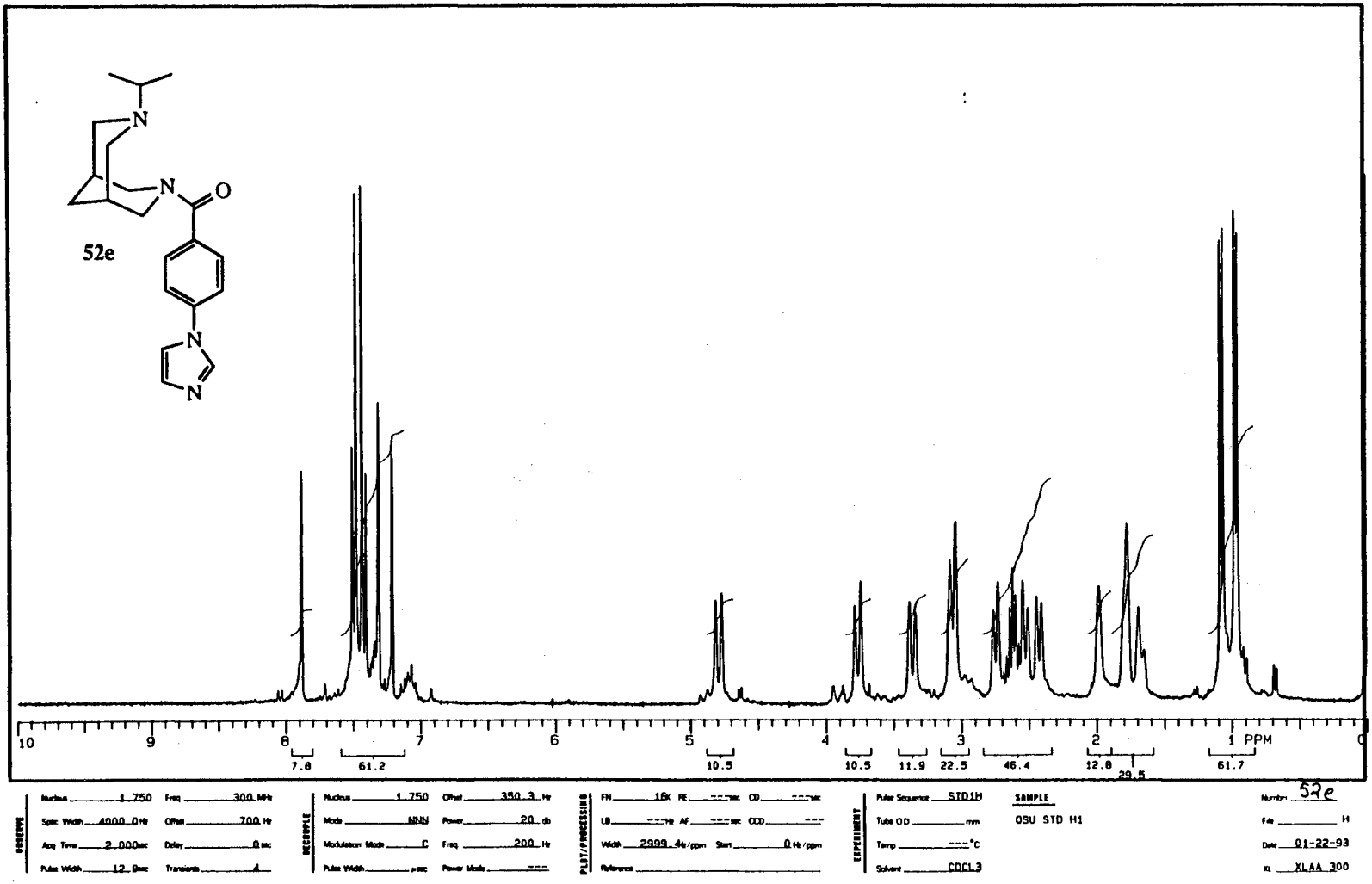
^{15}N NMR Spectrum of **52d**

Plate LXXI



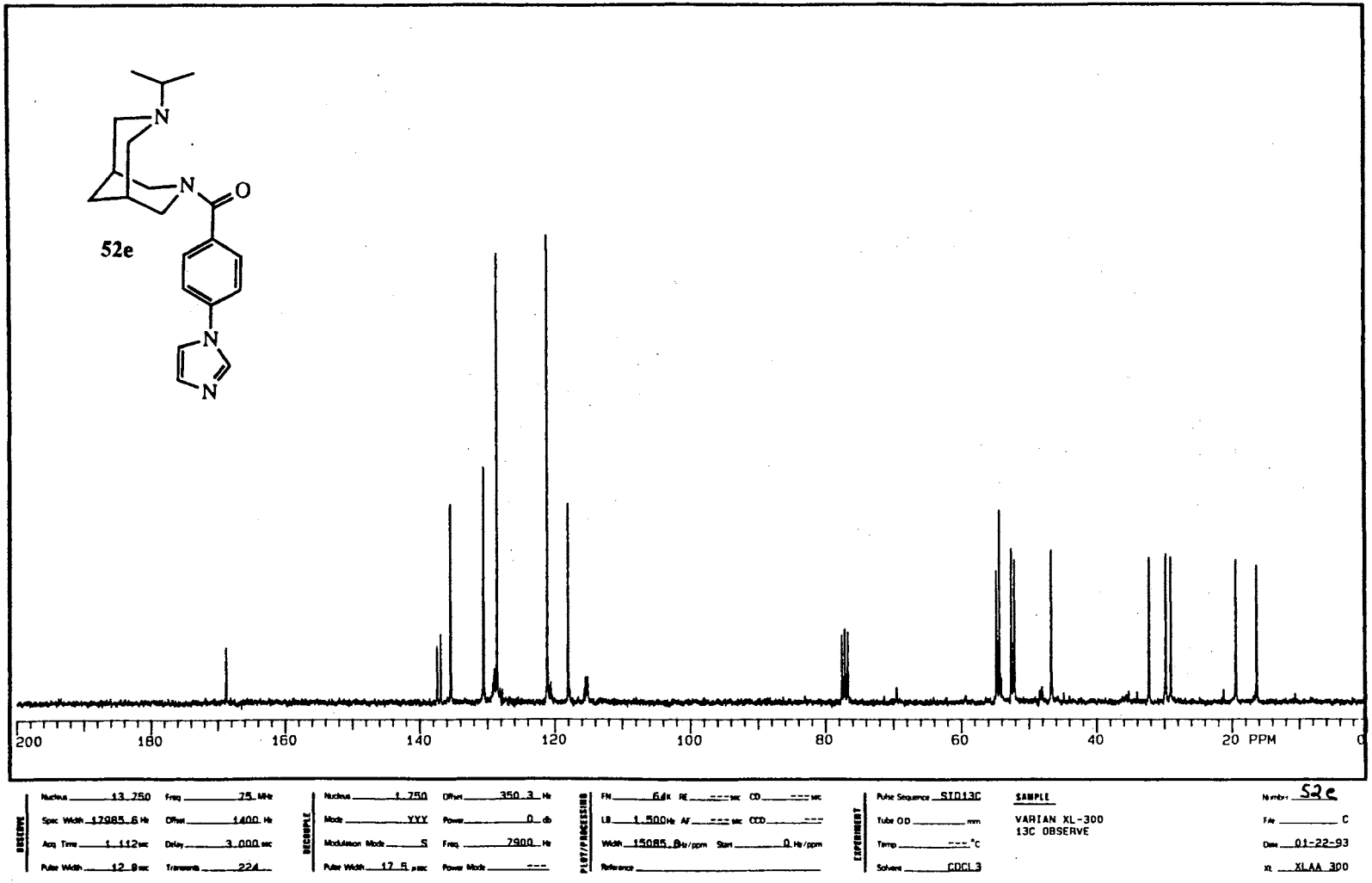
IR Spectrum of **52e**

Plate LXXII



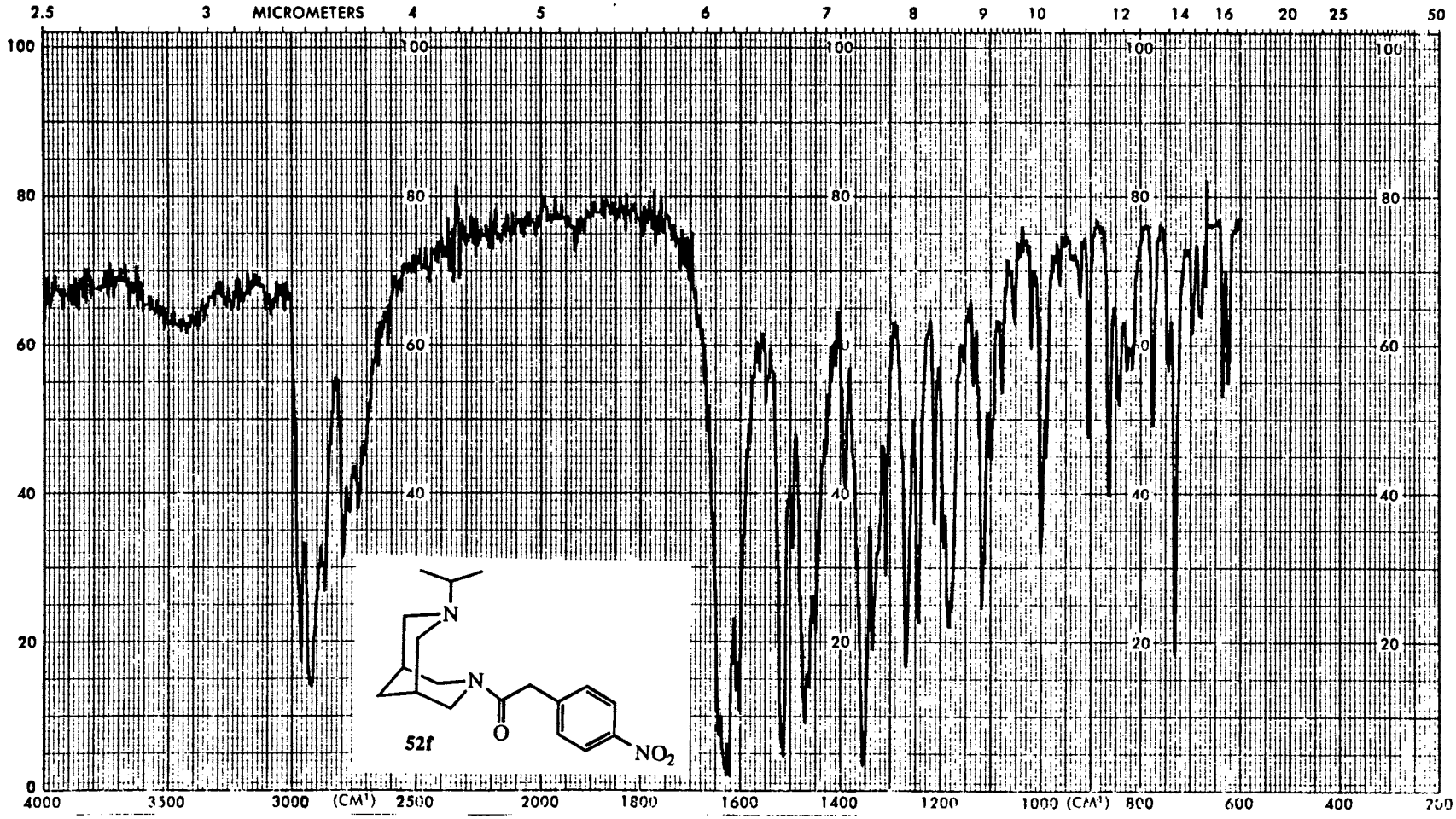
^{1}H NMR Spectrum of **52e**

Plate LXXIII



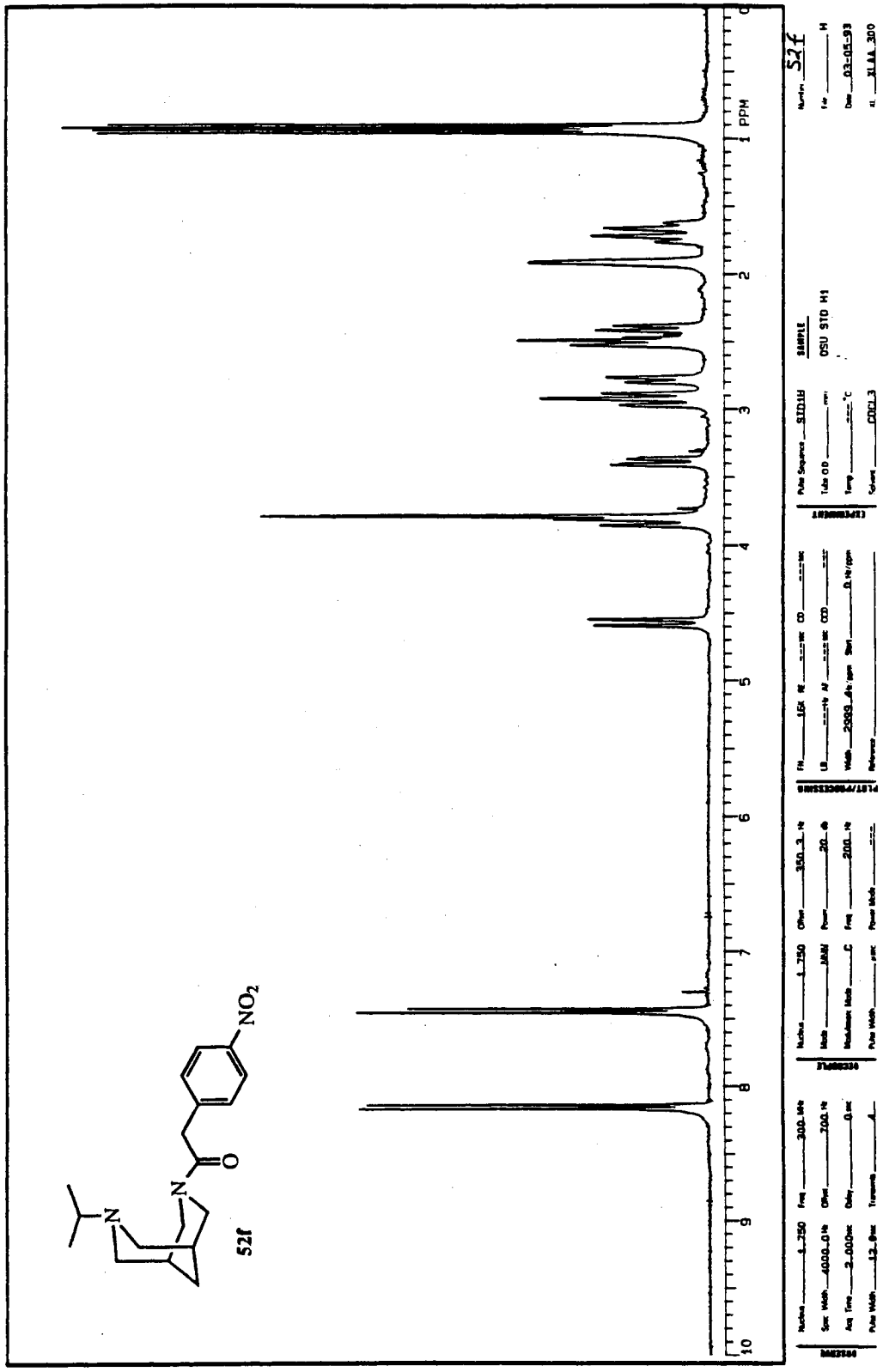
^{13}C NMR Spectrum of **52e**

Plate LXXIV



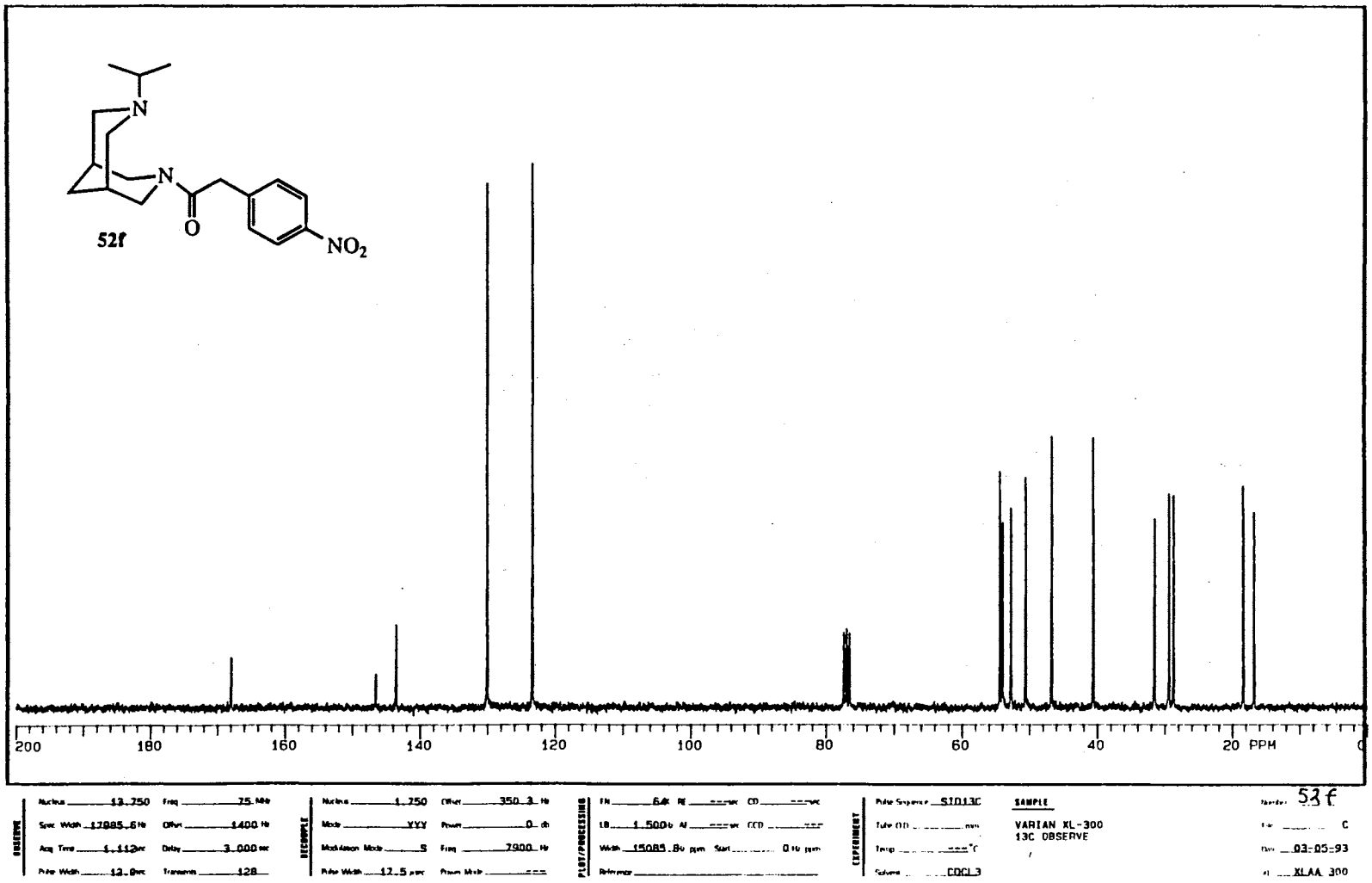
IR Spectrum of **52f**

Plate LXXV



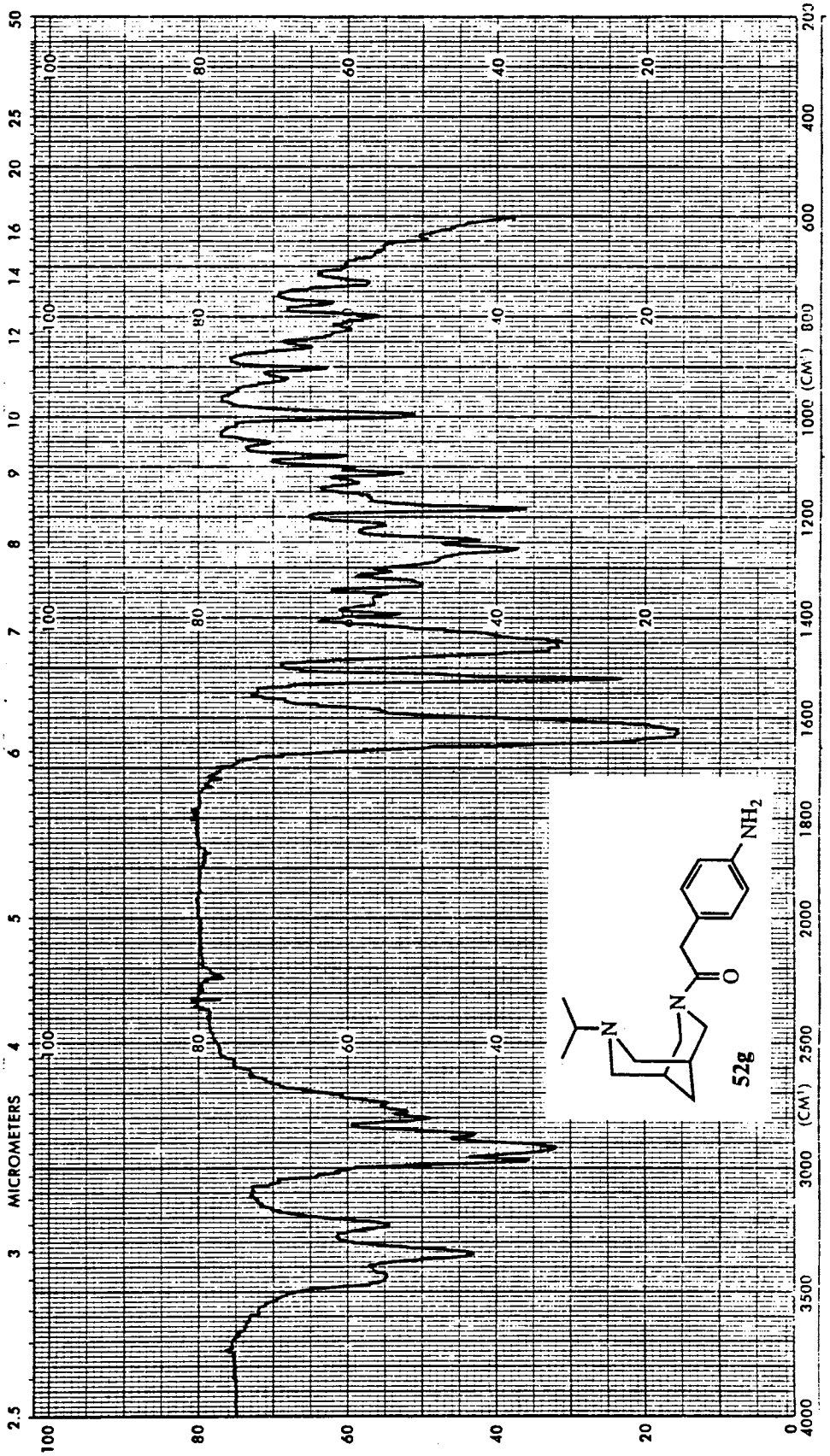
^{1}H NMR Spectrum of **52f**

Plate LXXVI



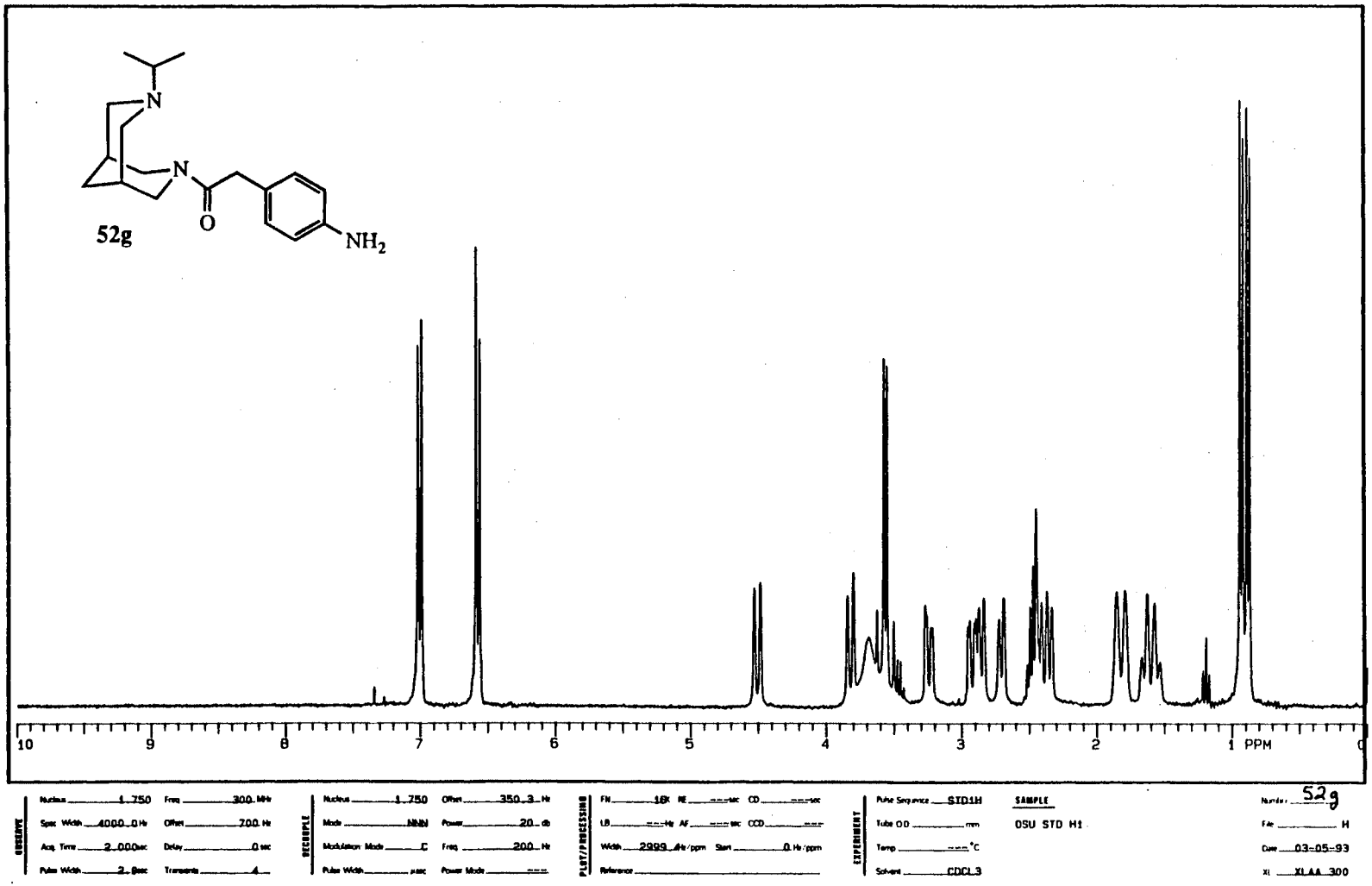
^{13}C NMR Spectrum of **52f**

Plate LXXVII



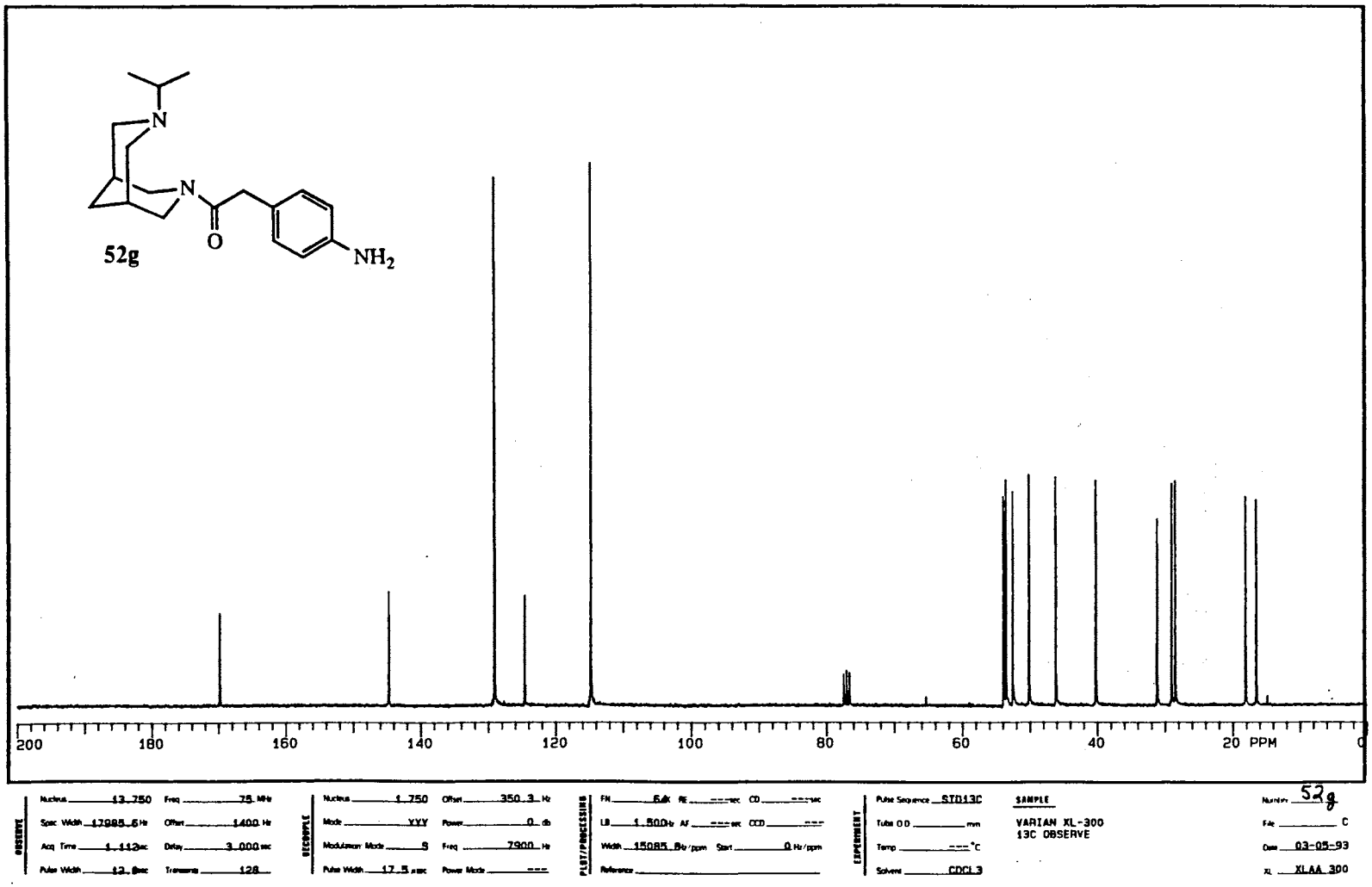
IR Spectrum of **52g**

Plate LXXVIII



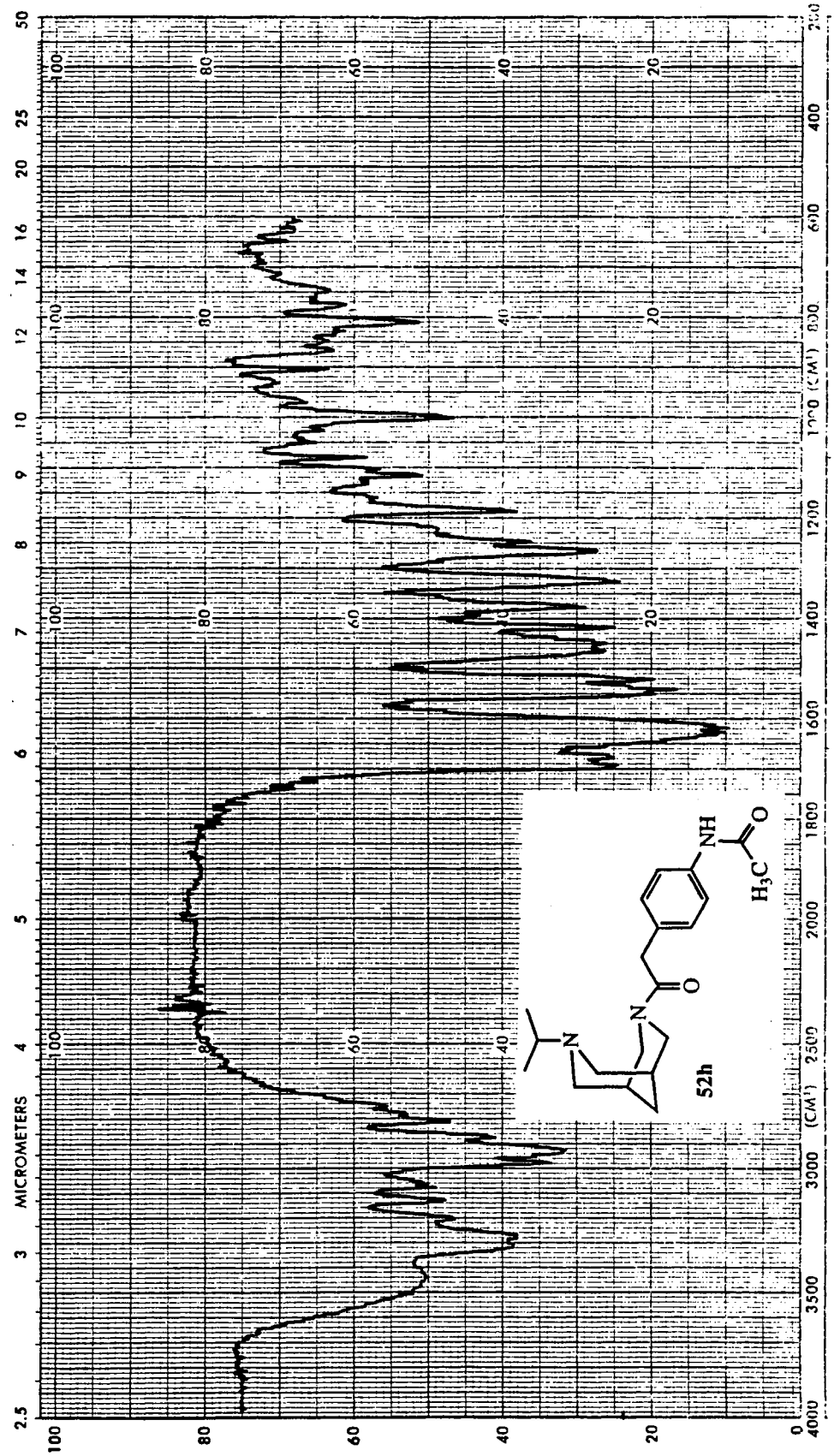
^{1}H NMR Spectrum of **52g**

Plate LXXIX



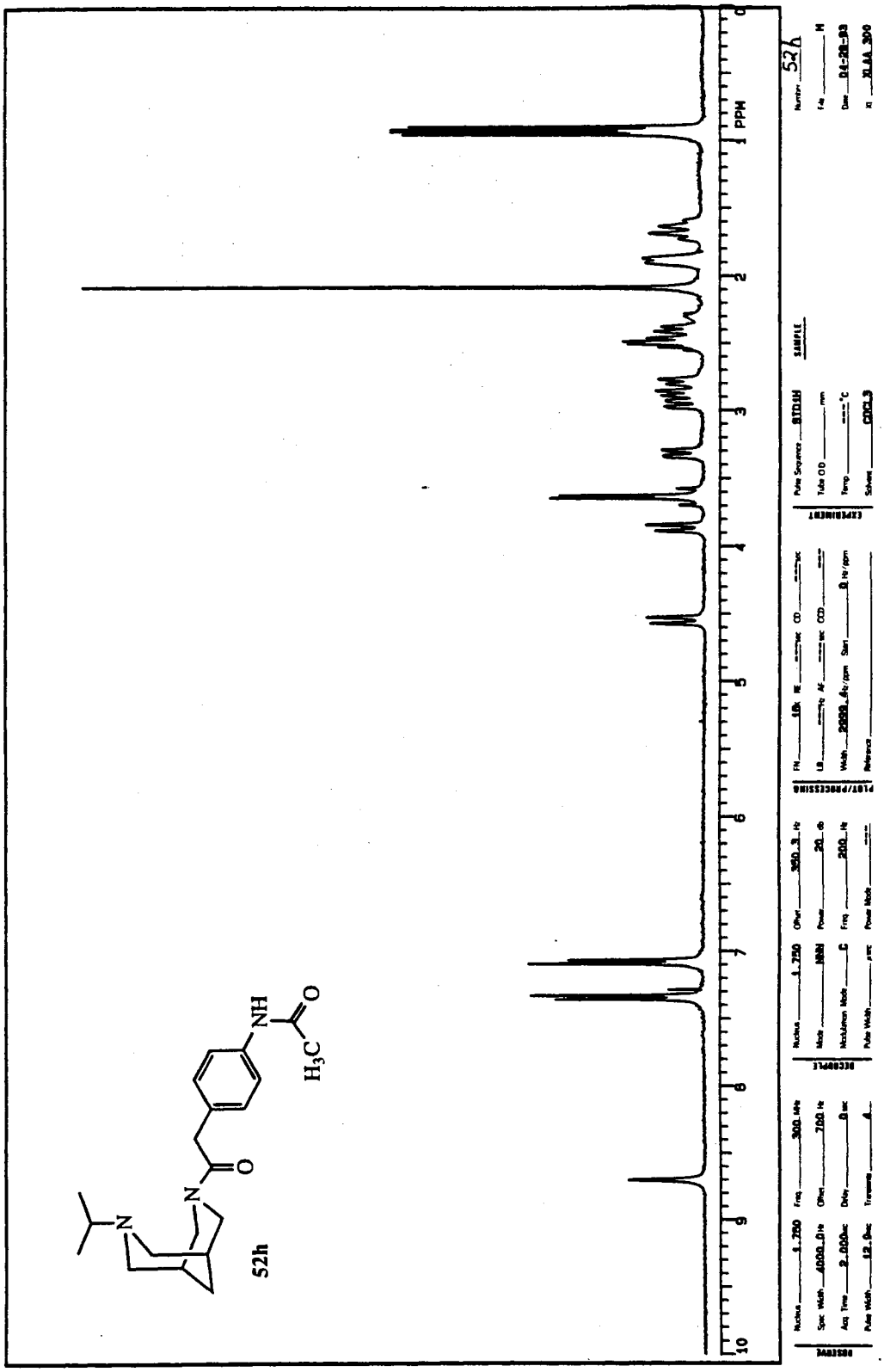
^{13}C NMR Spectrum of **52g**

Plate LXXX



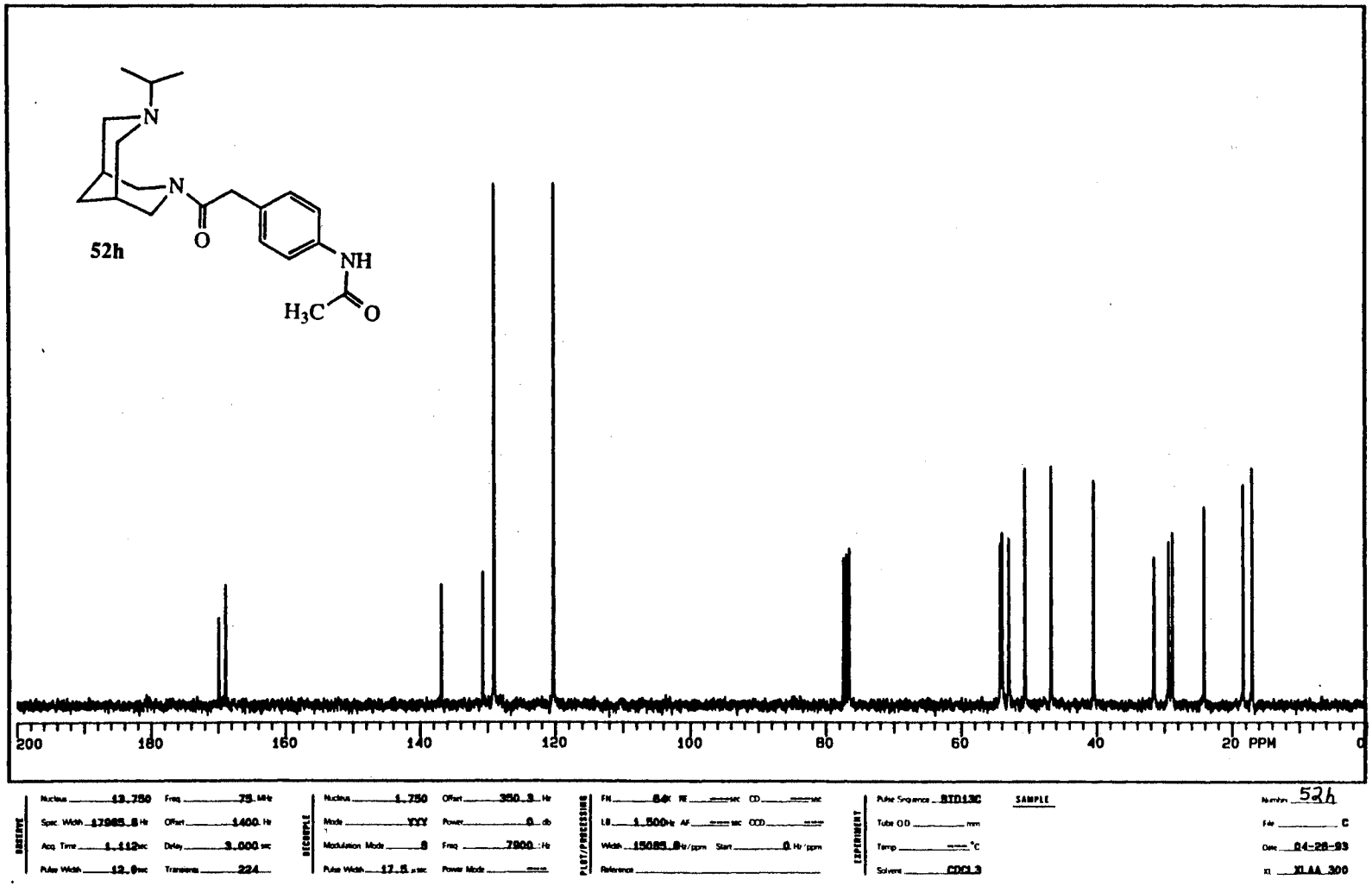
IR Spectrum of **52h**

Plate LXXXI



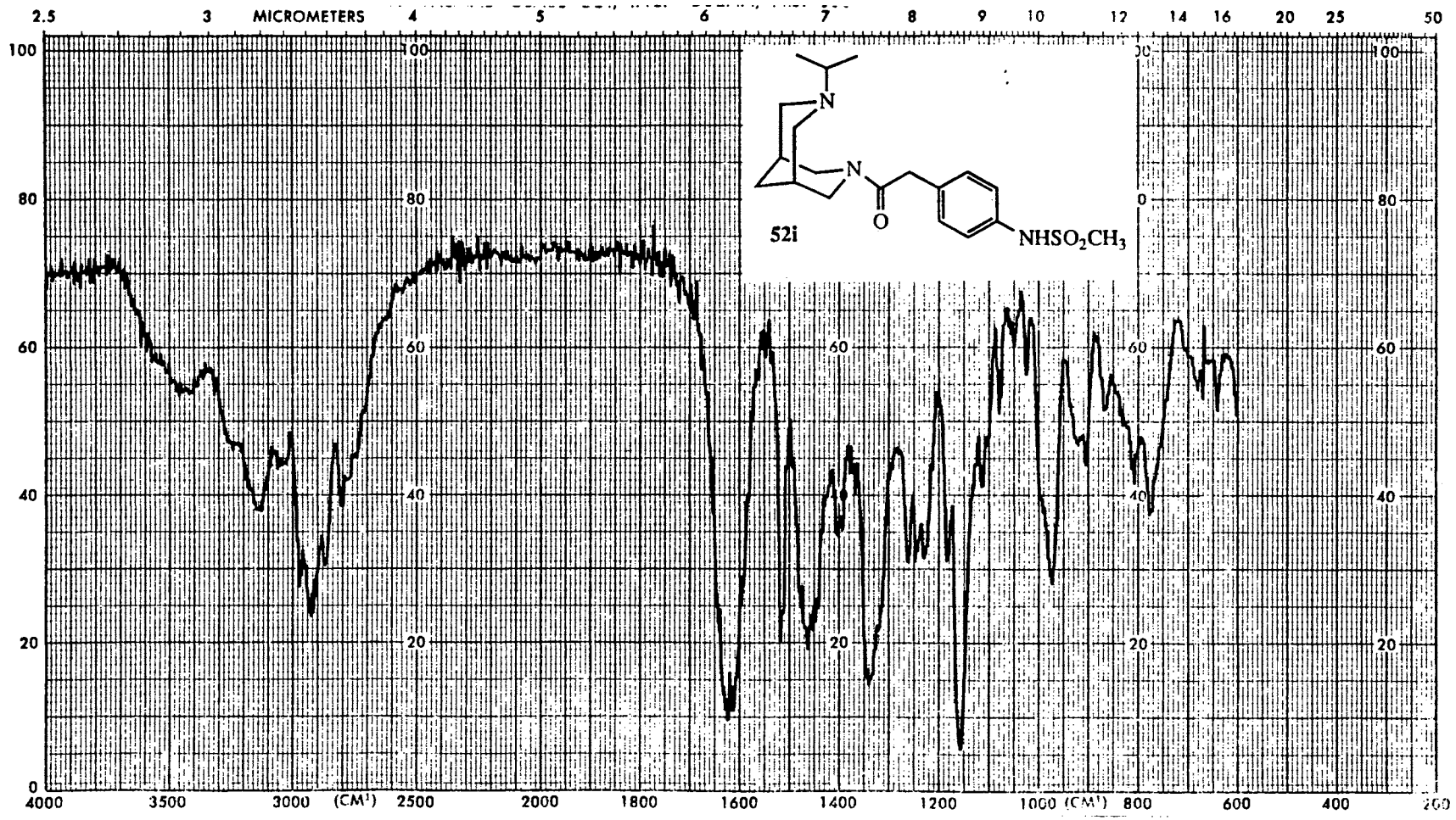
^{1}H NMR Spectrum of **52h**

Plate LXXXII



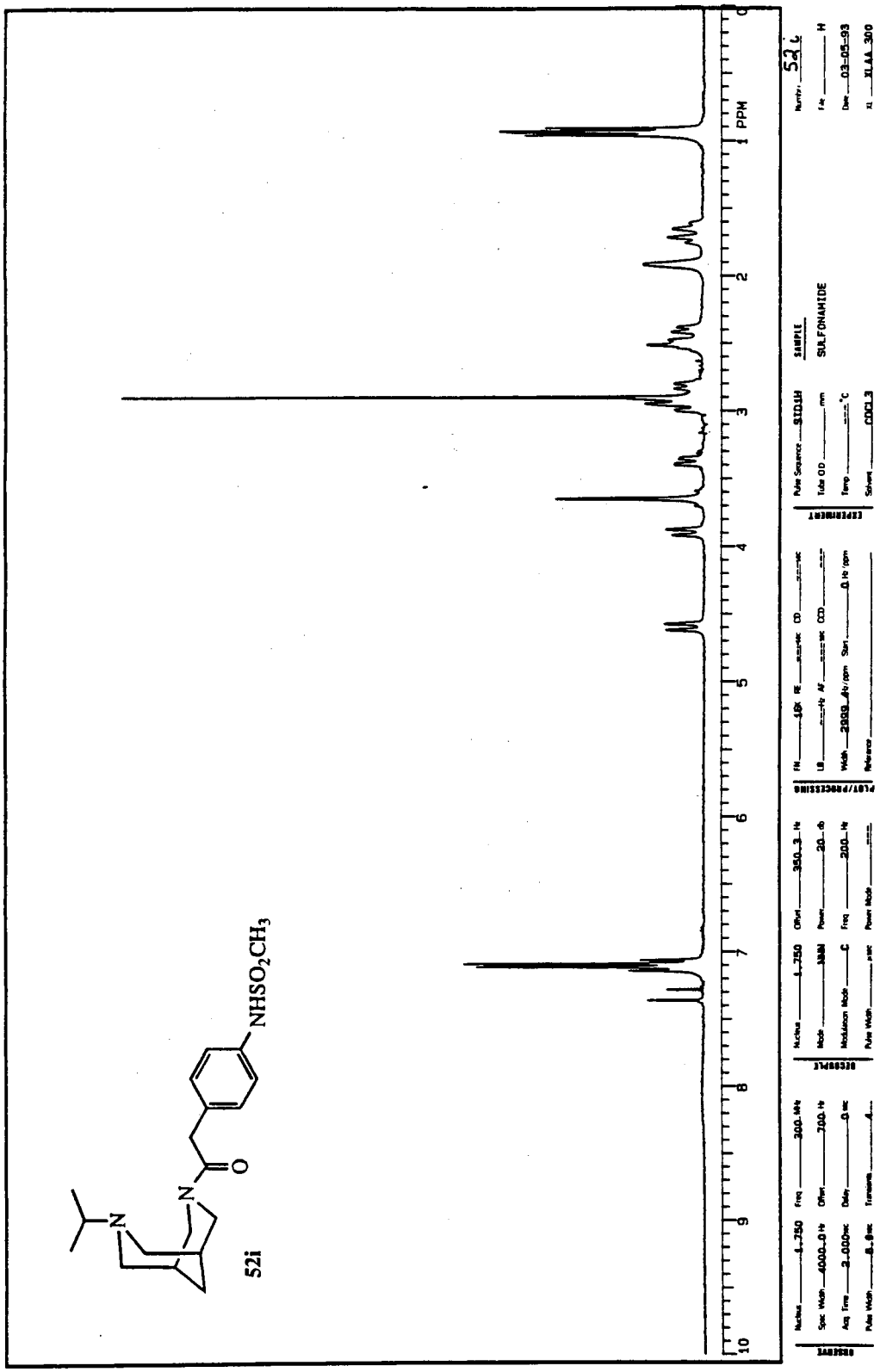
^{13}C NMR Spectrum of **52h**

Plate LXXXIII



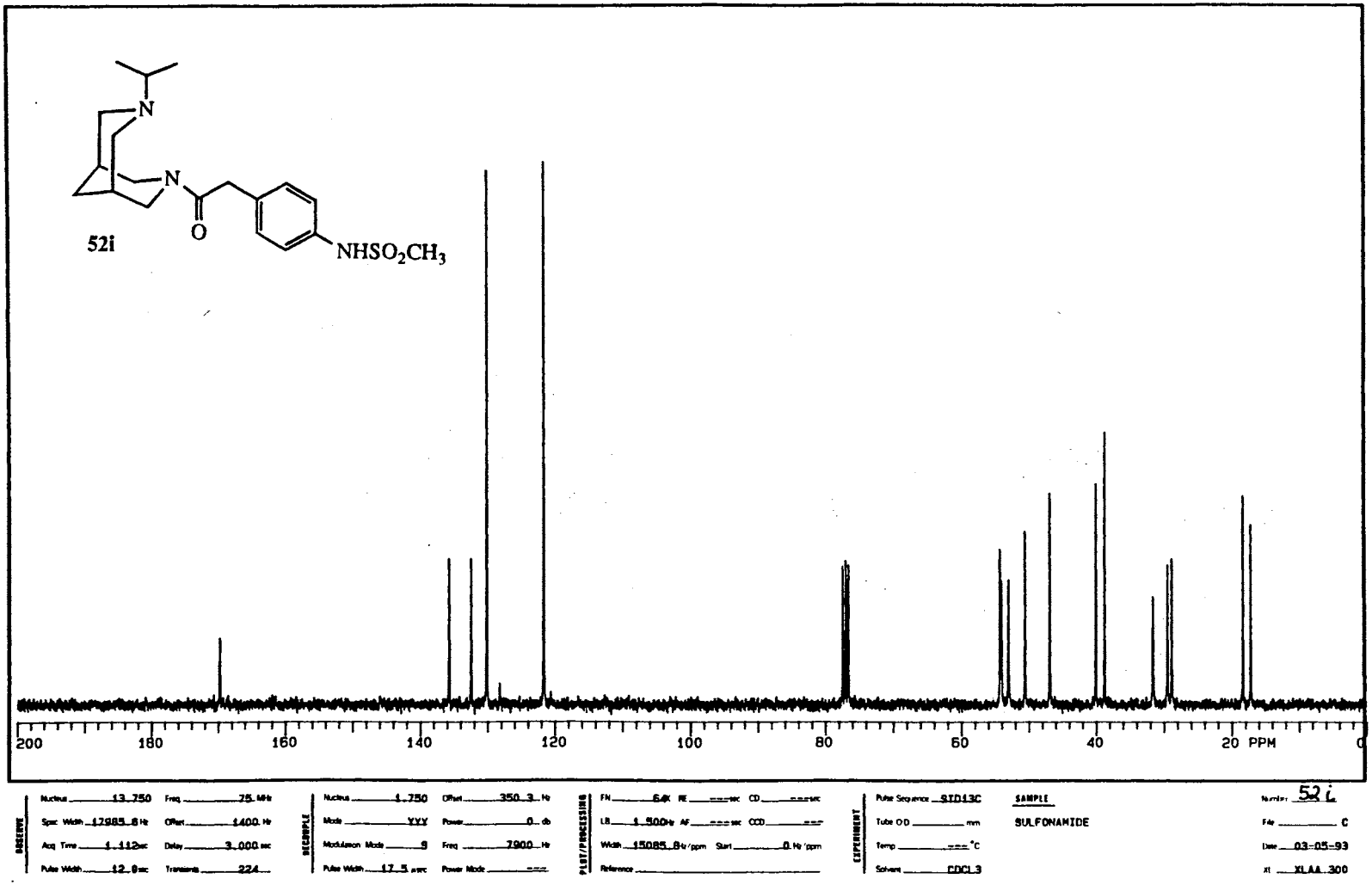
IR Spectrum of **52i**

Plate LXXXIV



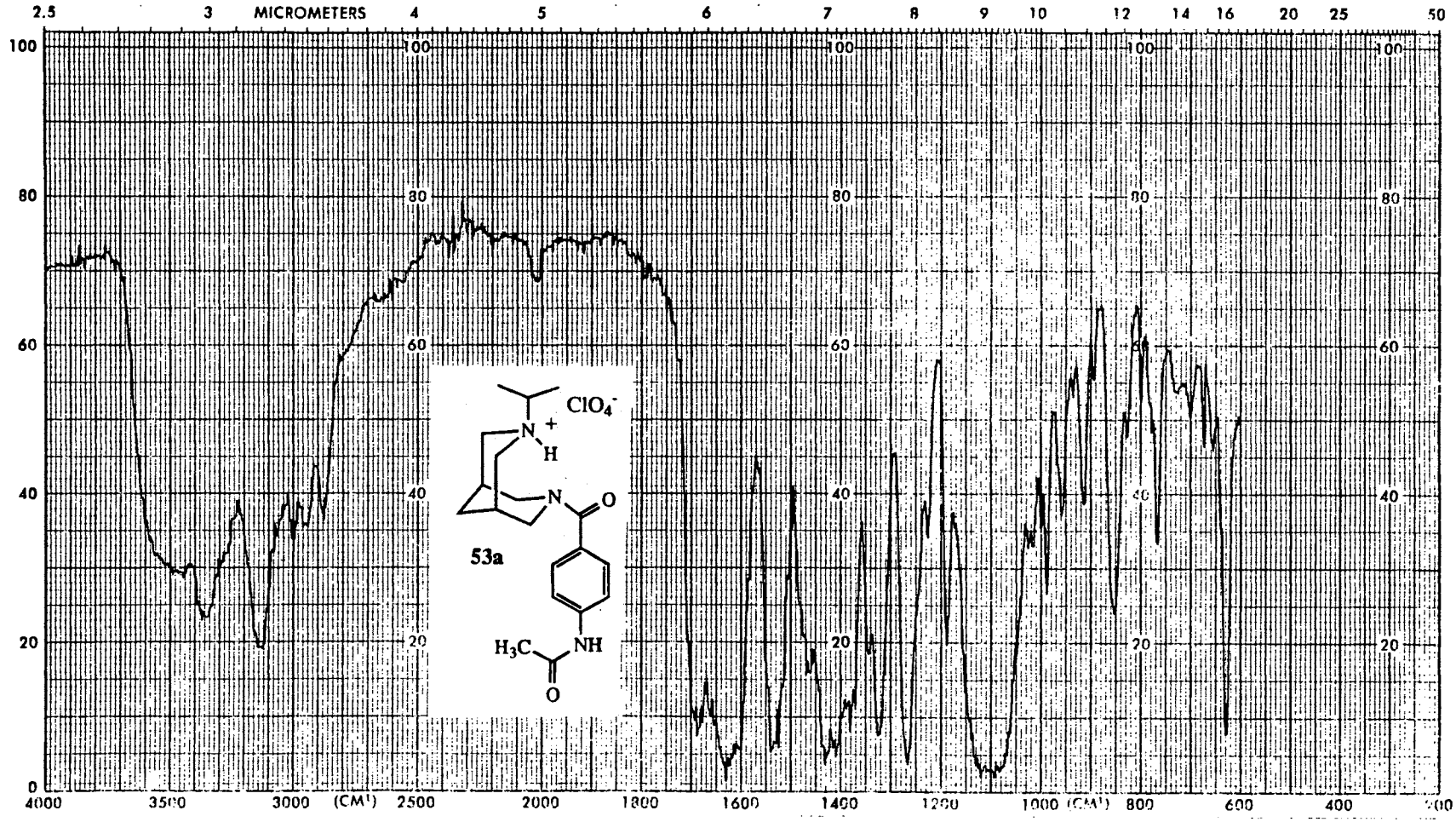
^{1}H NMR Spectrum of 52i

Plate LXXXV



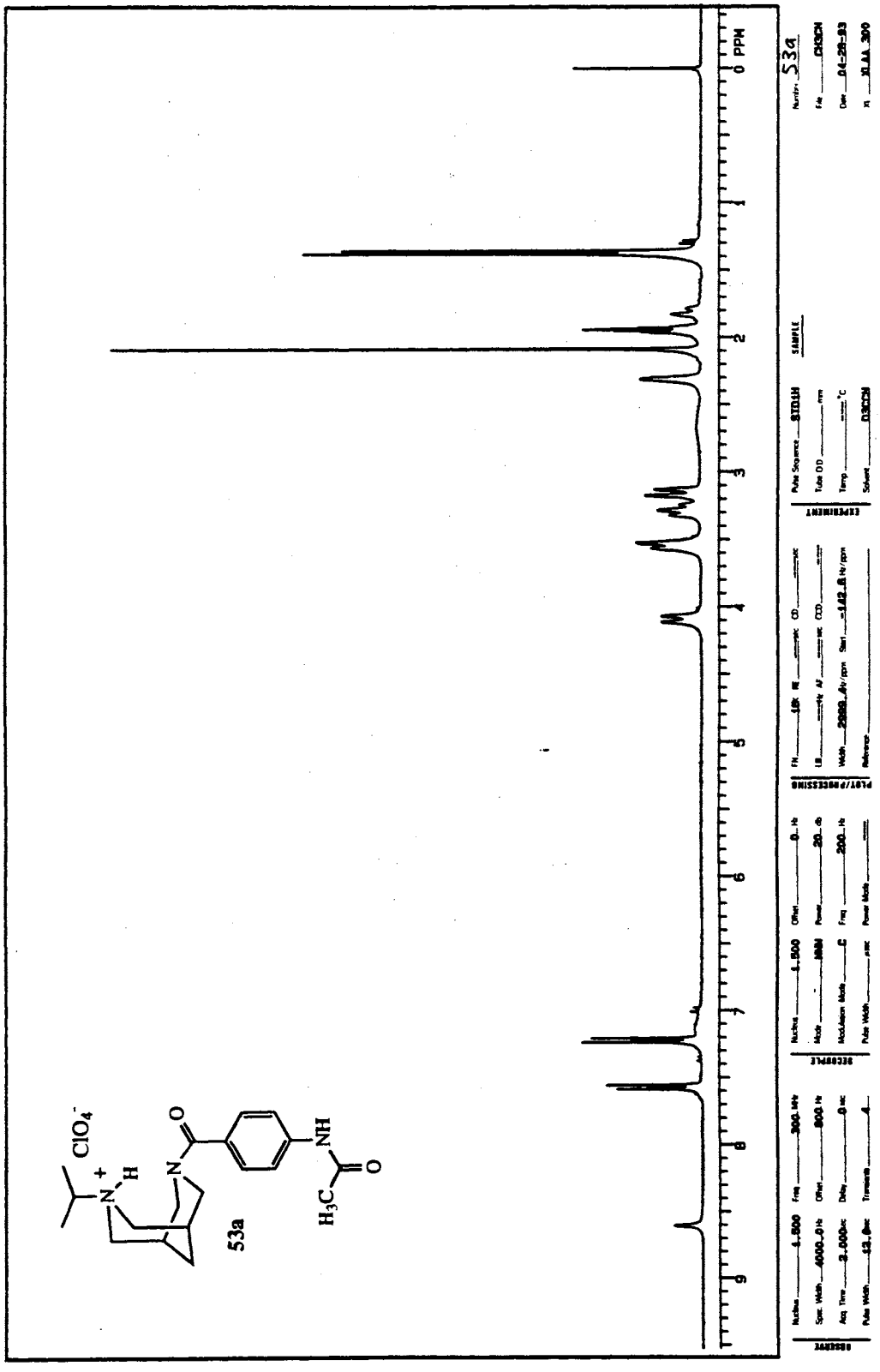
^{13}C NMR Spectrum of **52i**

Plate LXXXVI



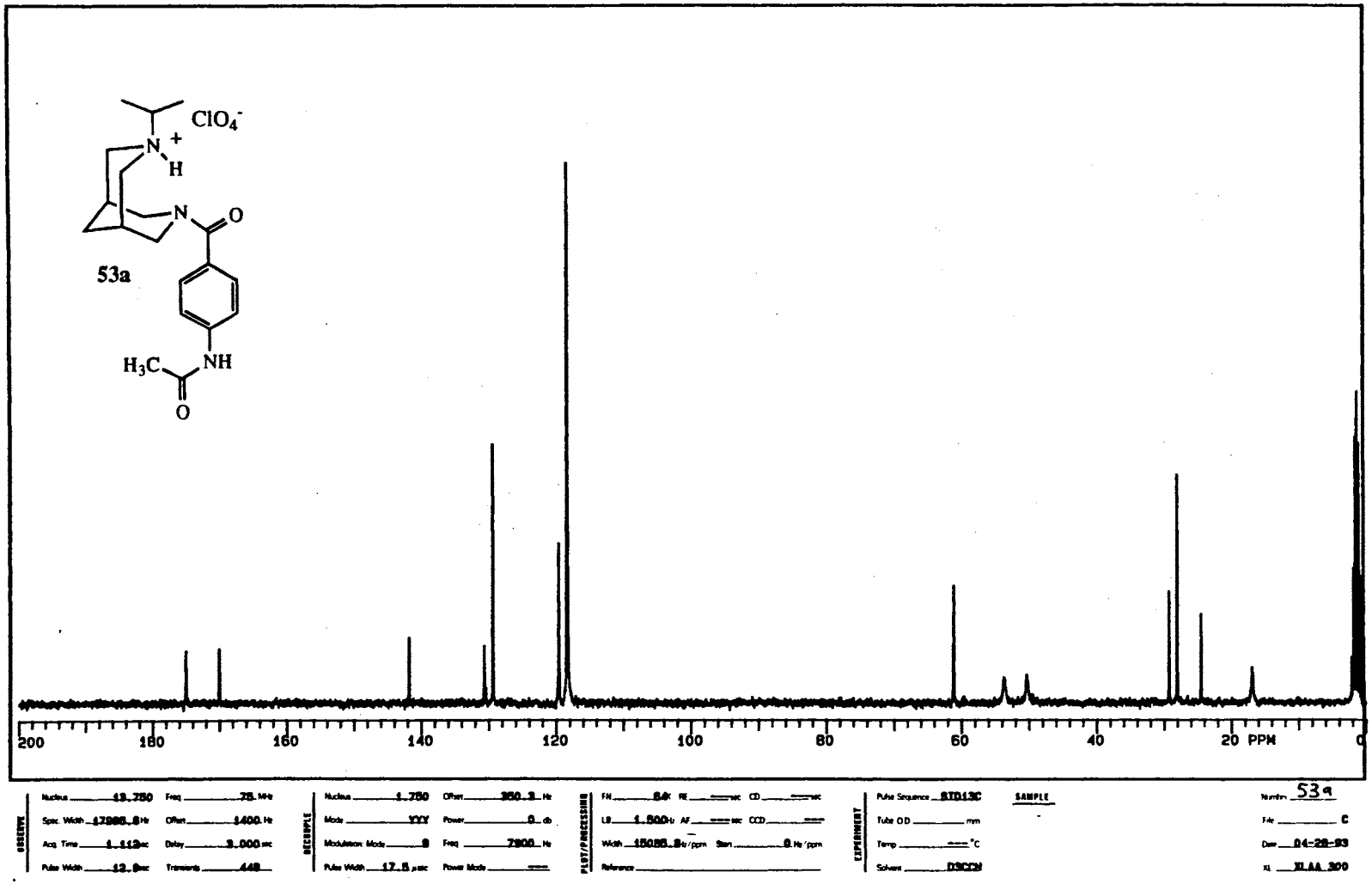
IR Spectrum of **53a**

Plate LXXXVII



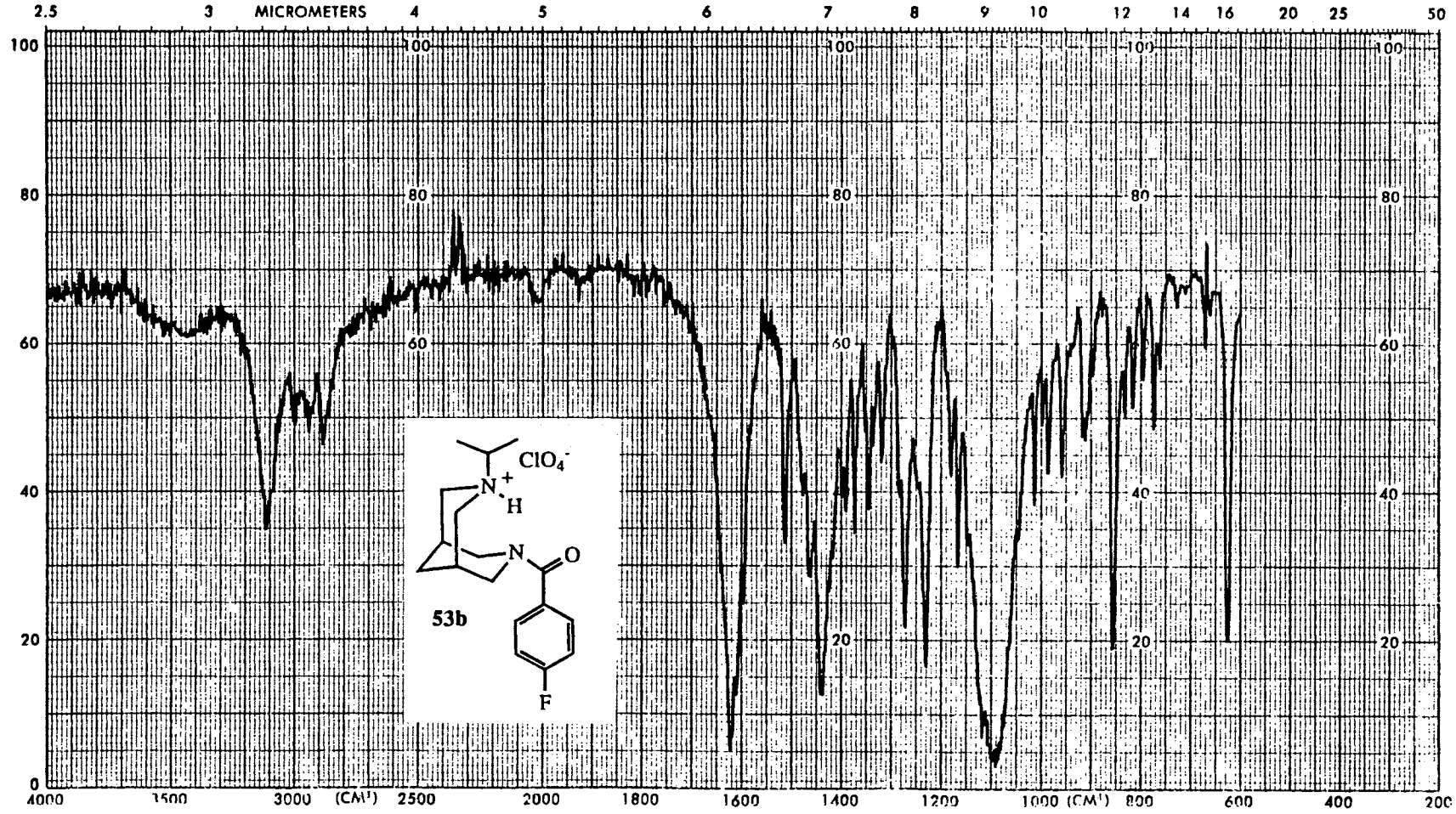
^{1}H NMR Spectrum of 53a

Plate LXXXVIII



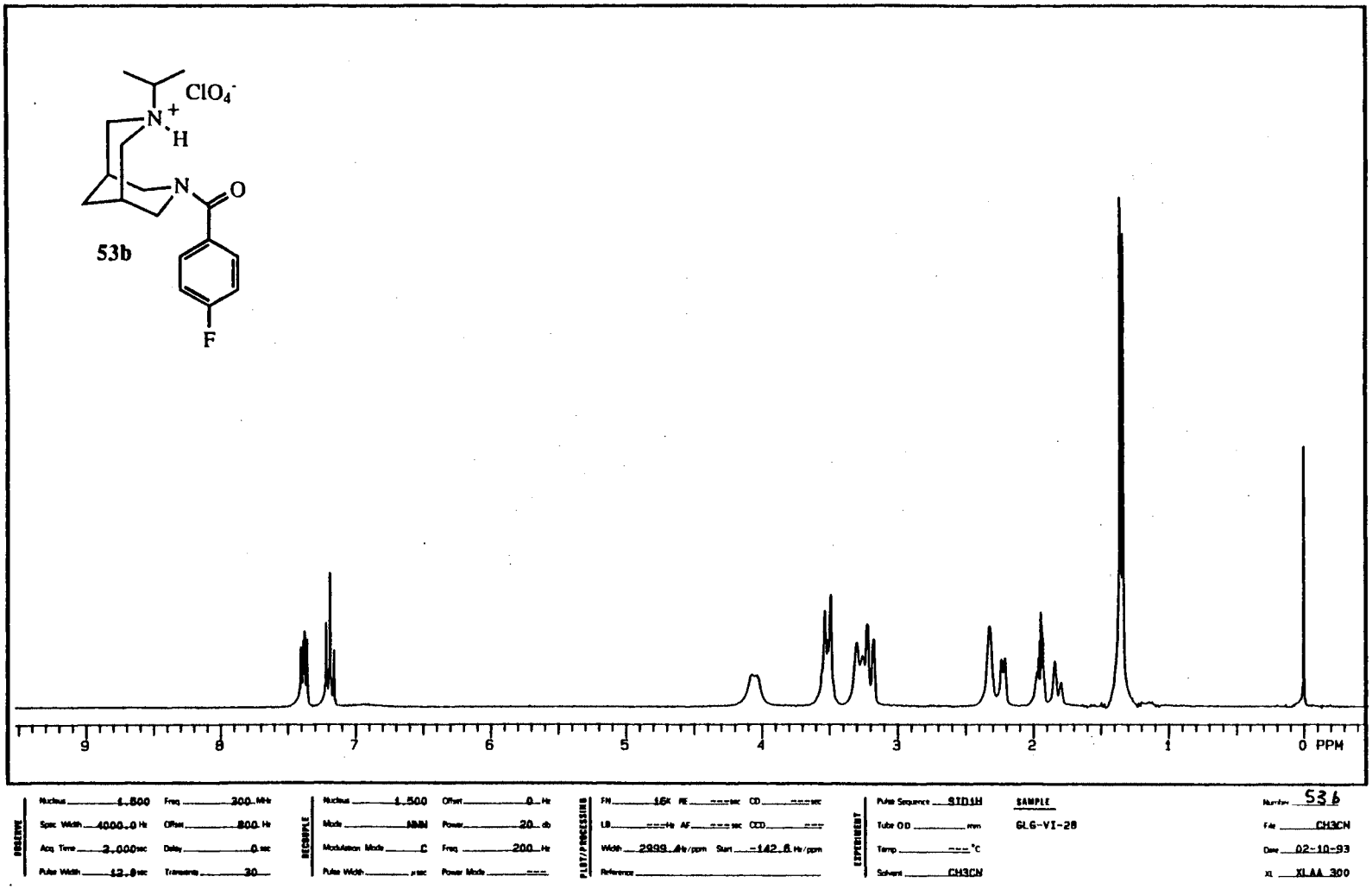
^{13}C NMR Spectrum of **53a**

Plate LXXXIX



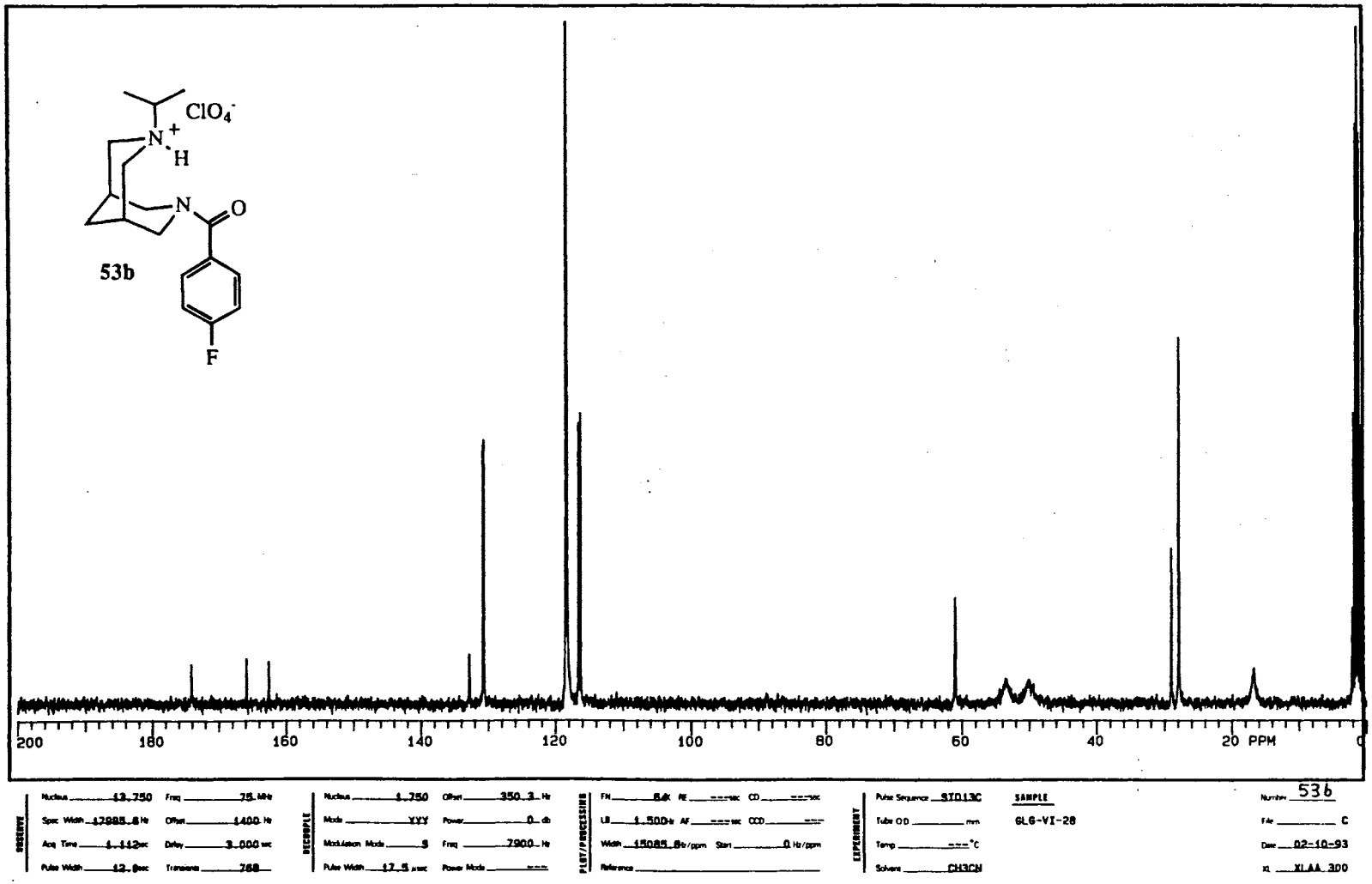
IR Spectrum of **53b**

Plate XC



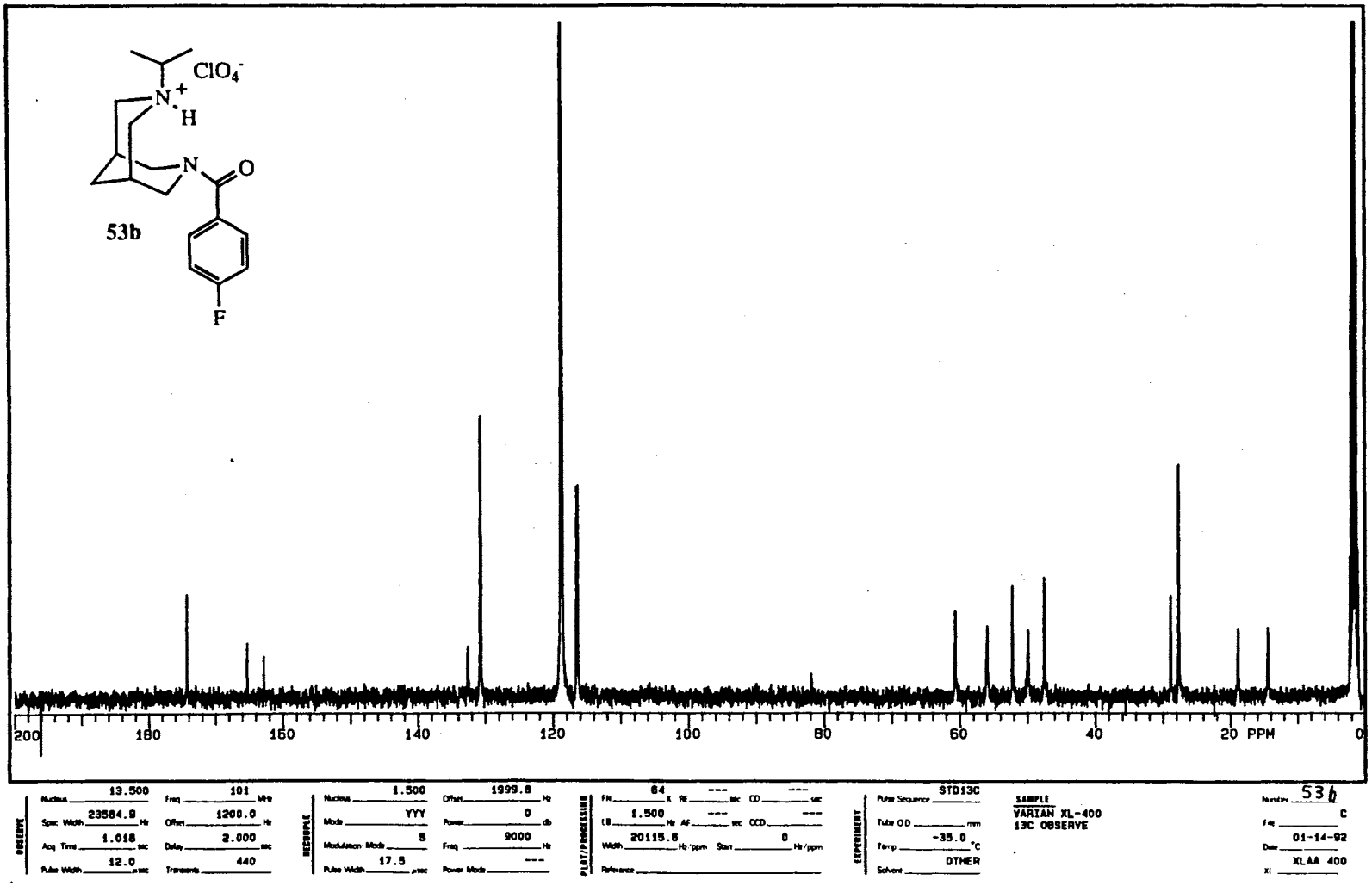
^{1}H NMR Spectrum of **53b**

Plate XCI



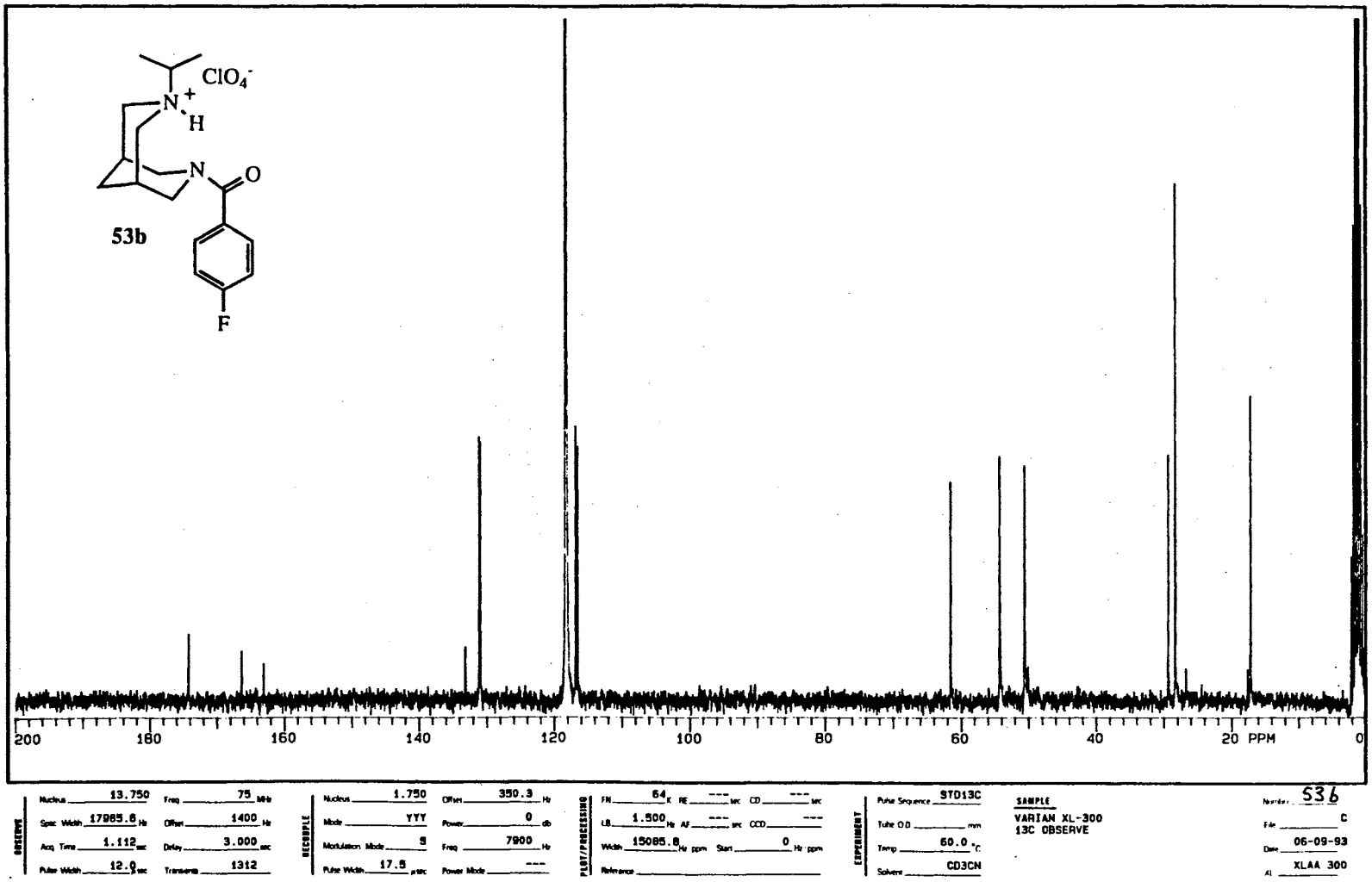
^{13}C NMR Spectrum (RT) of **53b**

Plate XCII



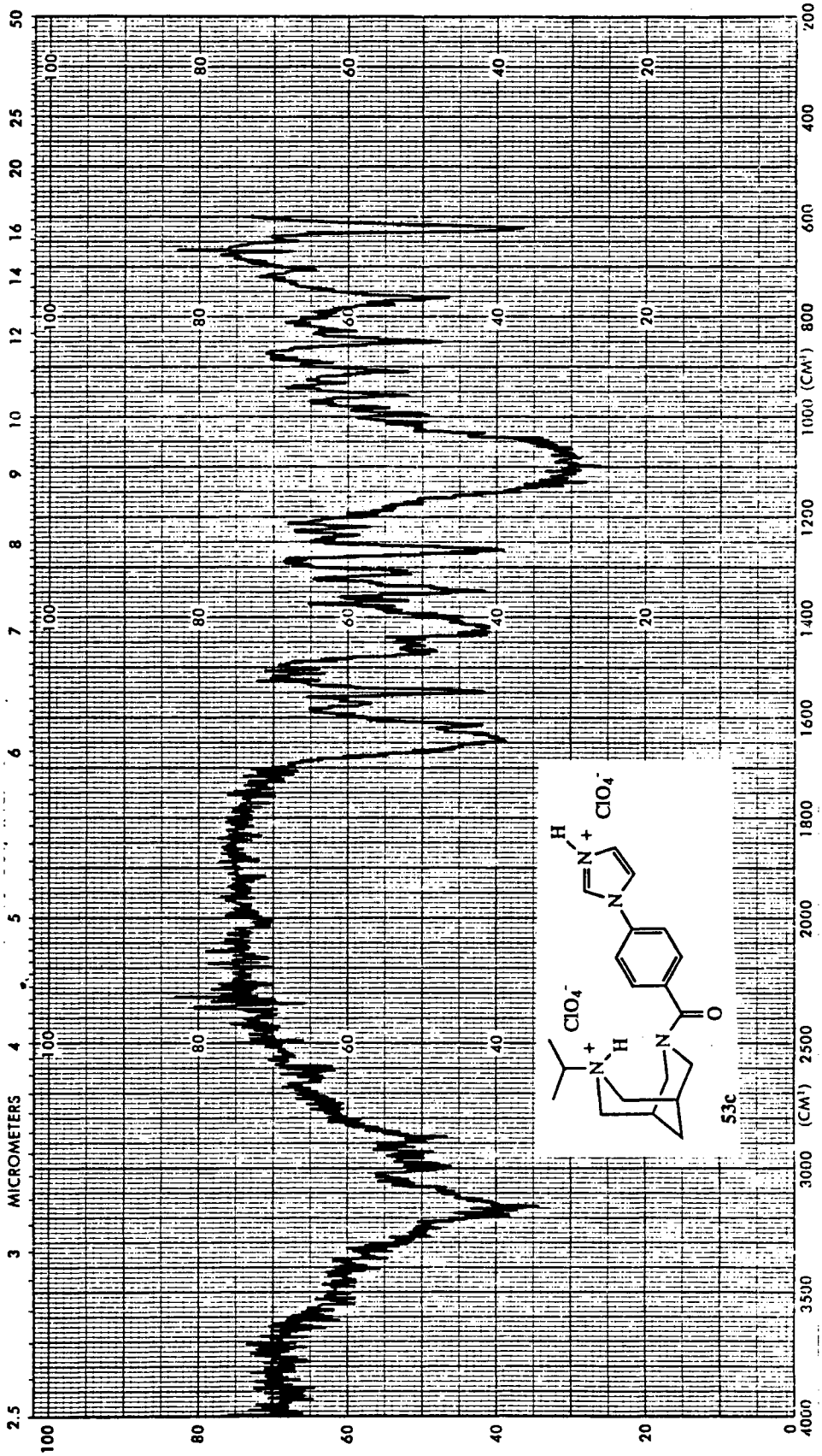
^{13}C NMR Spectrum (-35°C) of **53b**

Plate XCIII



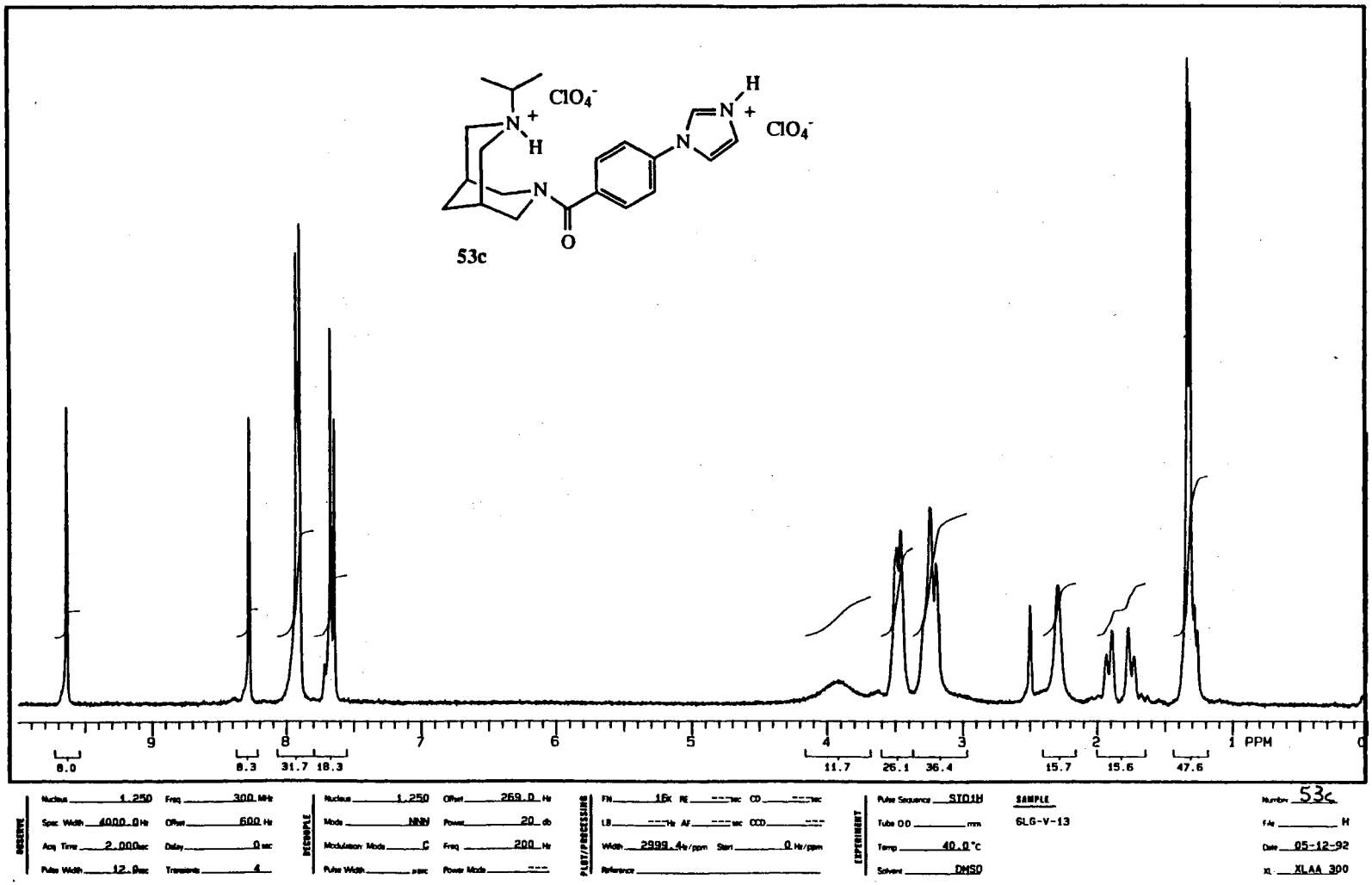
^{13}C NMR Spectrum (60°C) of **53b**

Plate XCIV



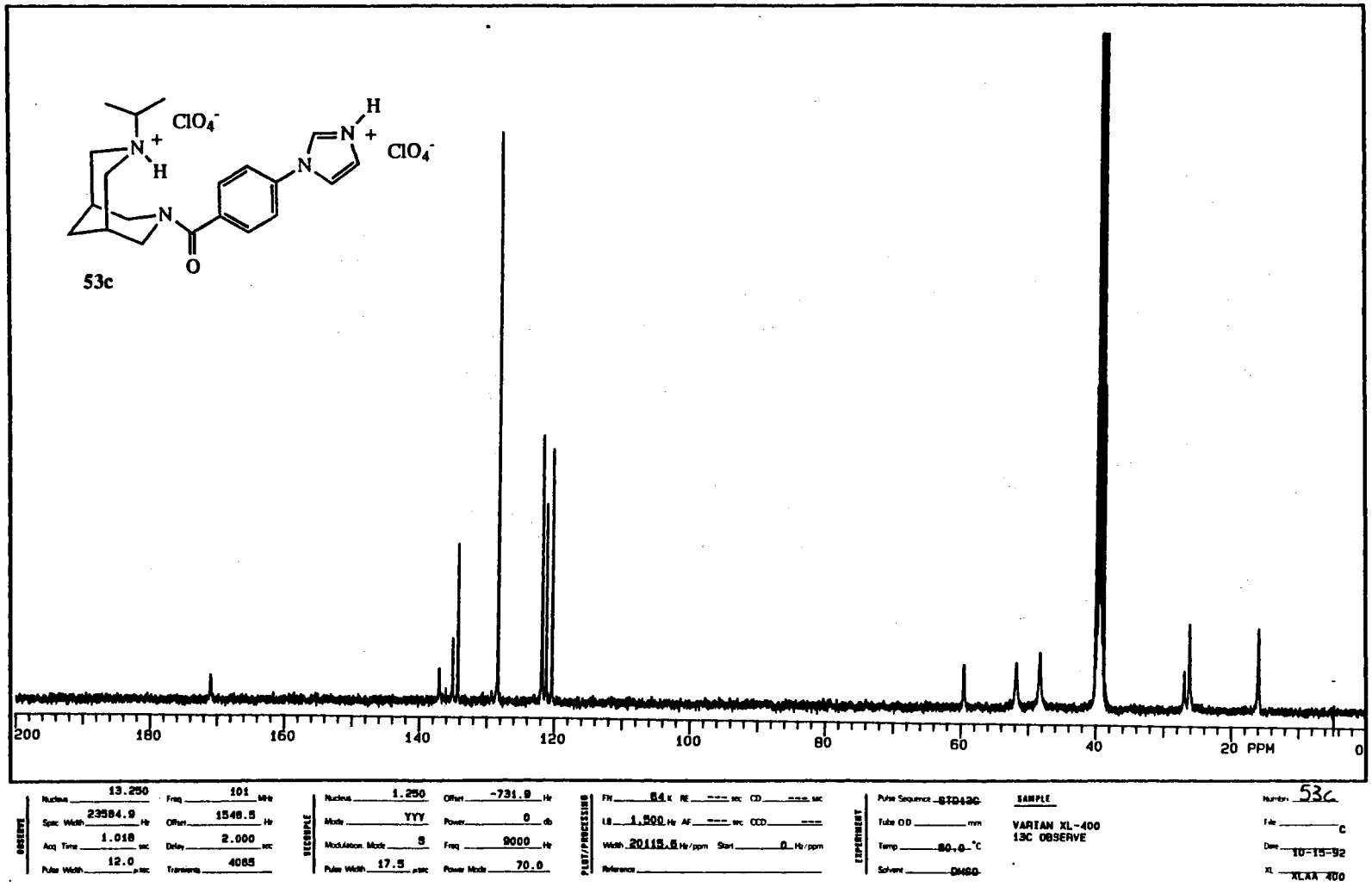
IR Spectrum of 53c

Plate XCV



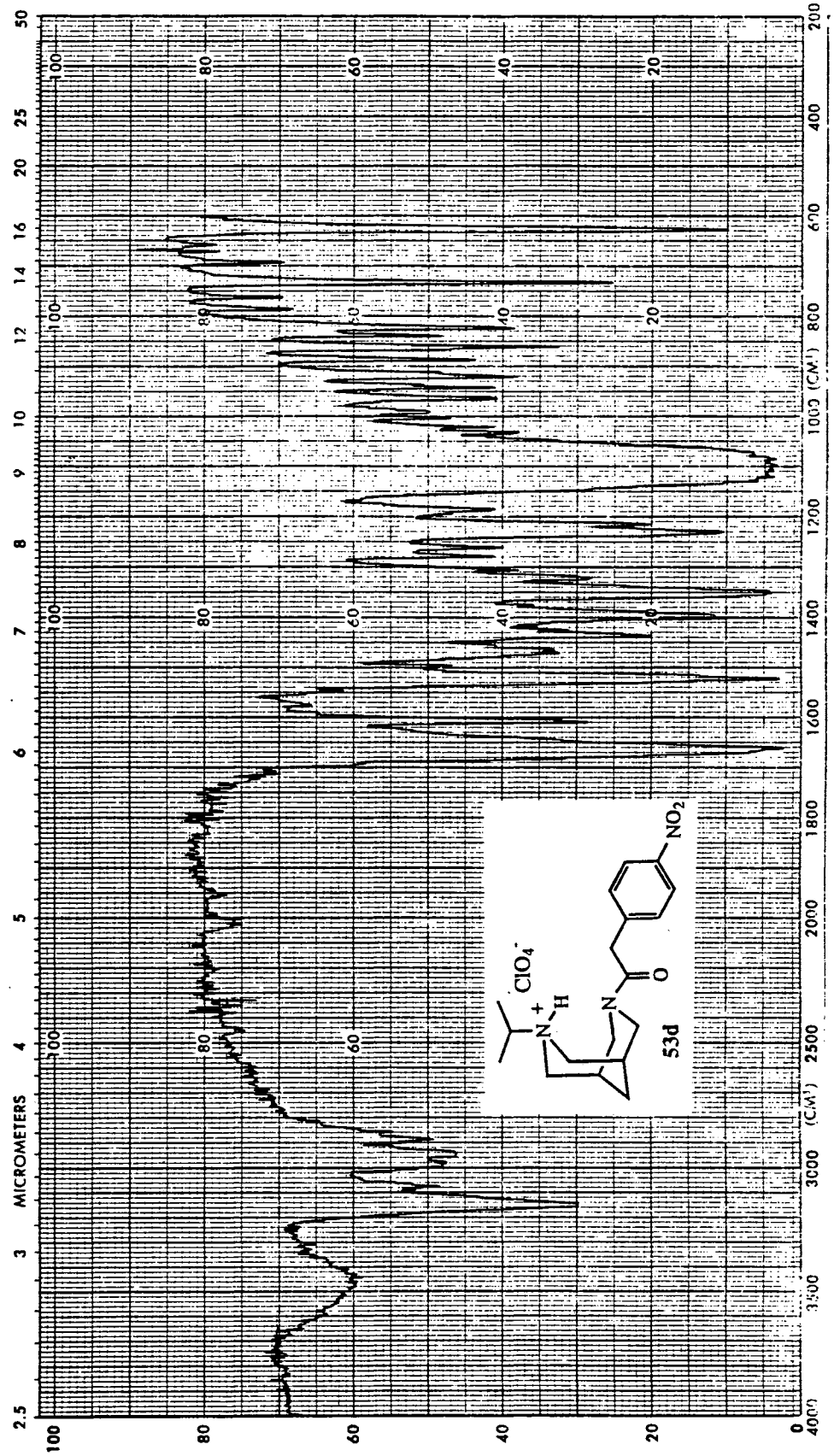
^{1}H NMR Spectrum of **53c**

Plate XCVI



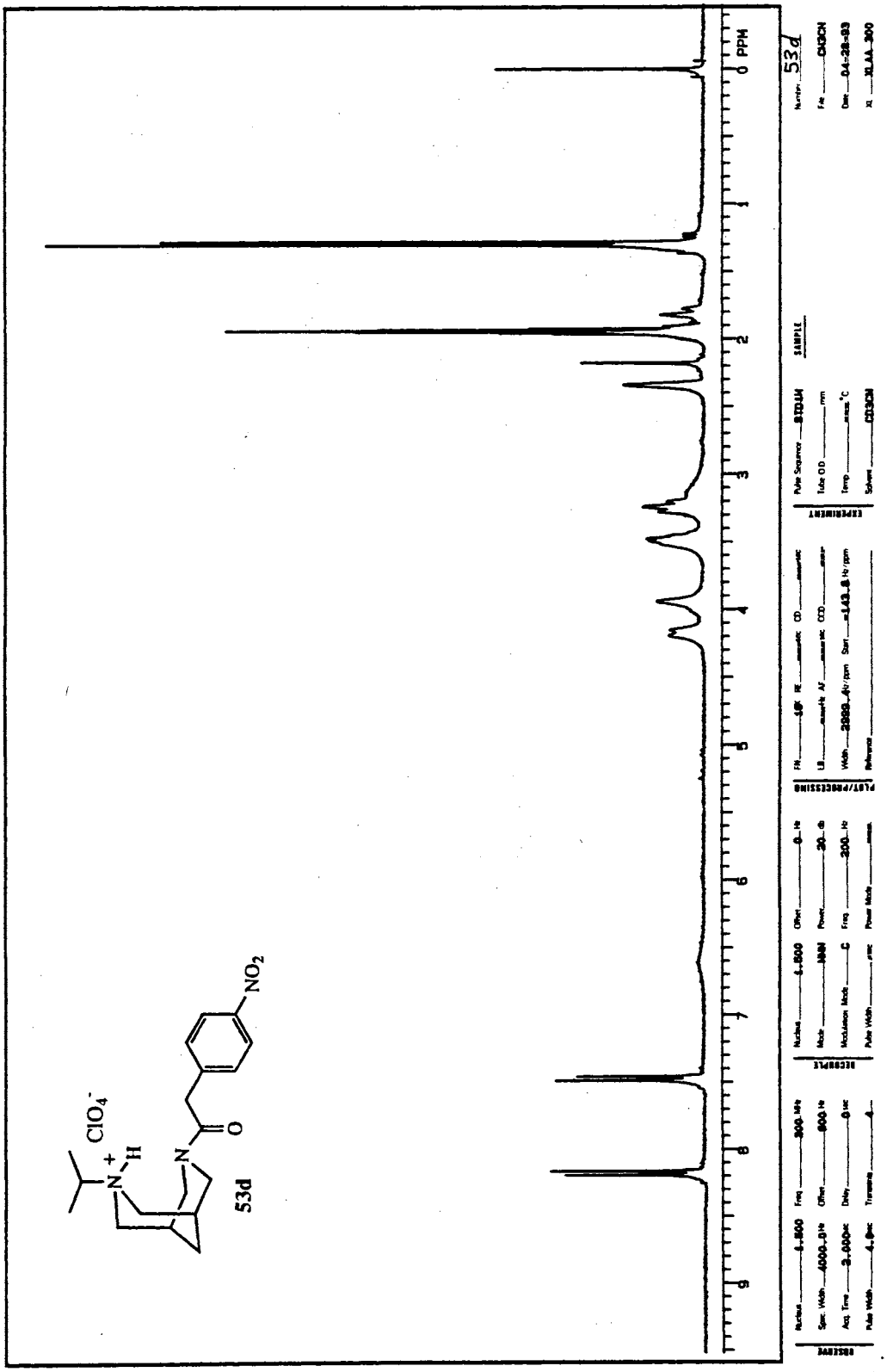
^{13}C NMR Spectrum of **53c**

Plate XCVII



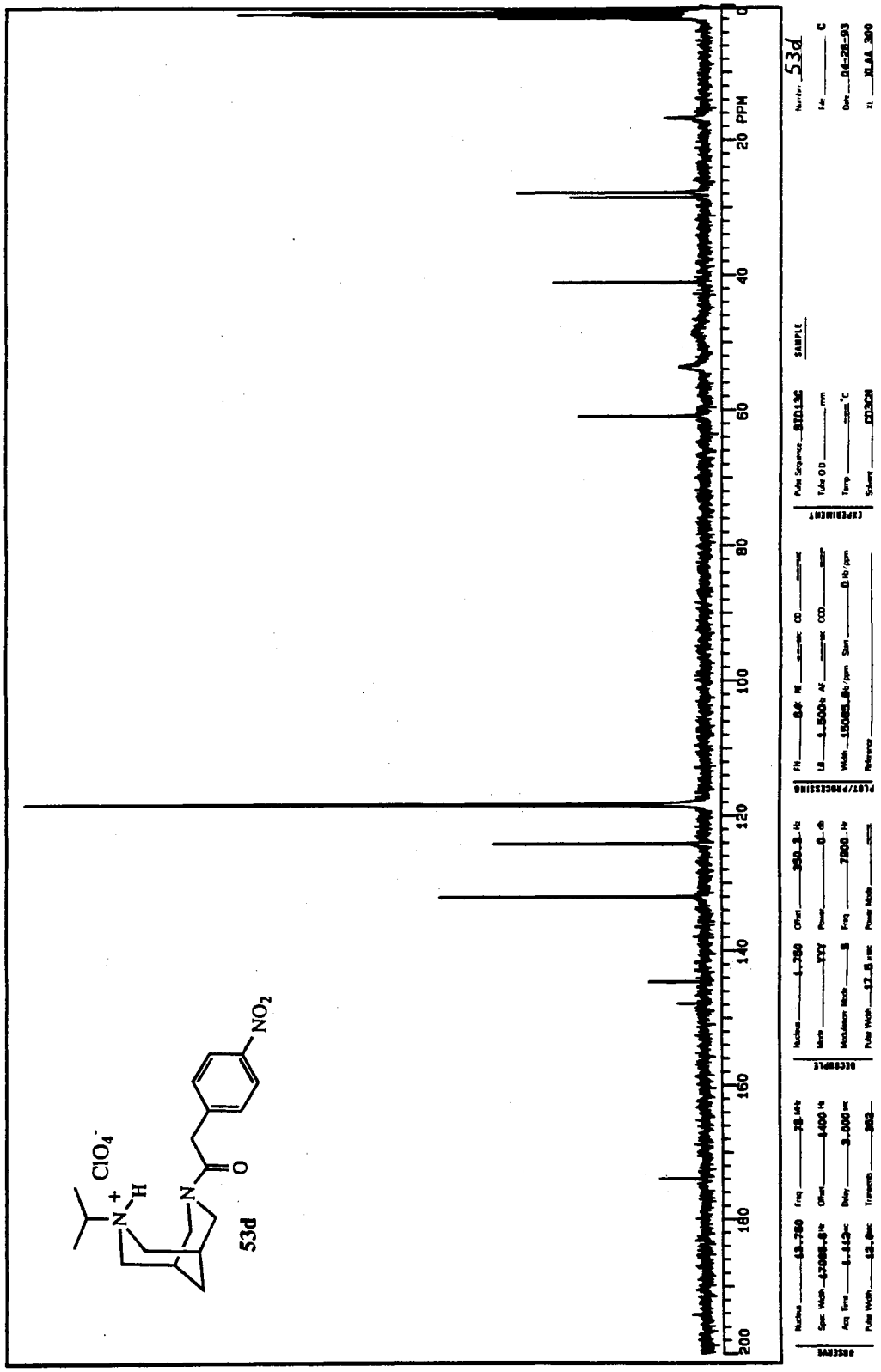
IR Spectrum of 53d

Plate XCVIII



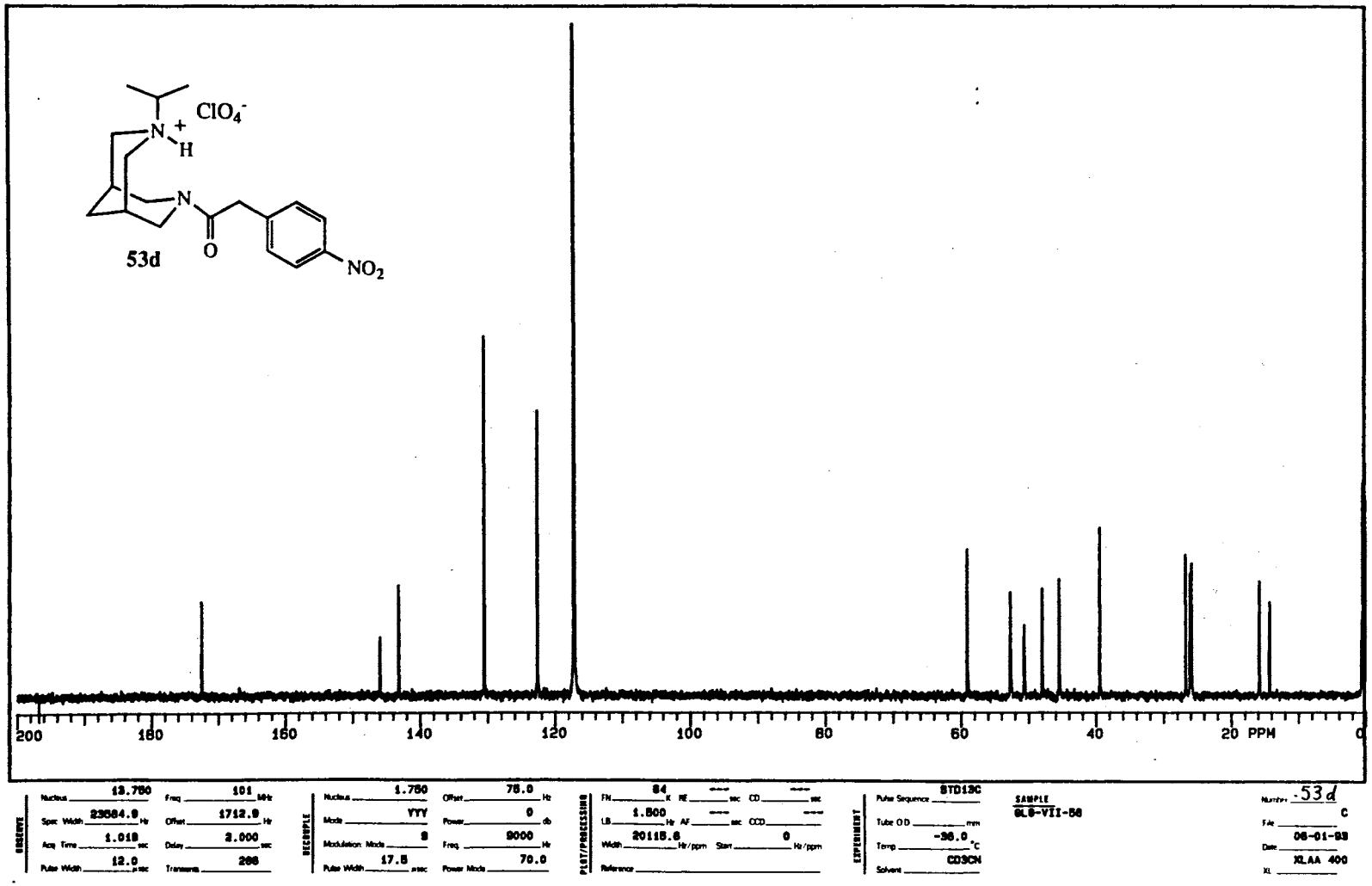
^{1}H NMR Spectrum of 53d

Plate XCIX



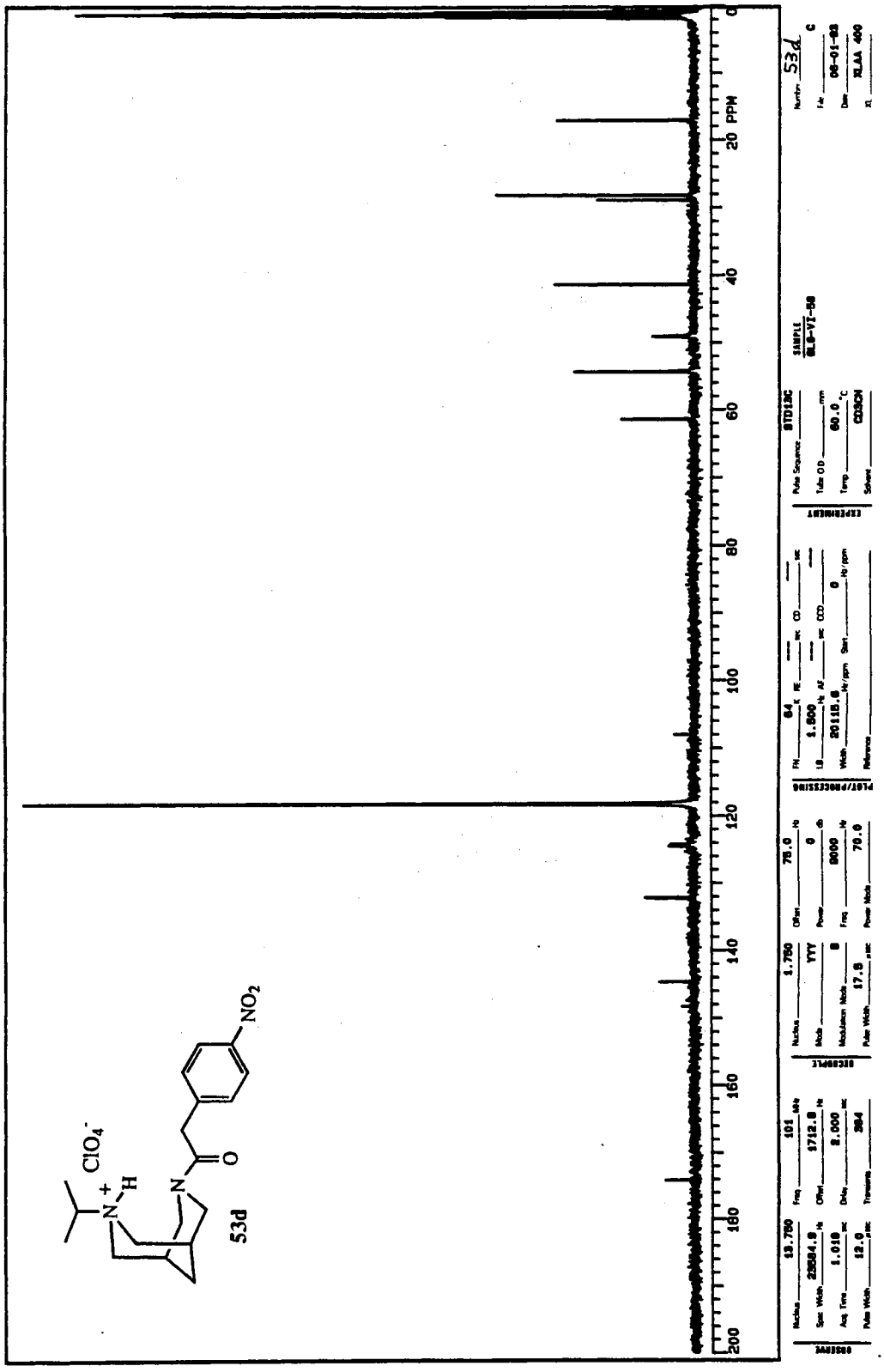
^{13}C NMR Spectrum (RT) of **53d**

Plate C



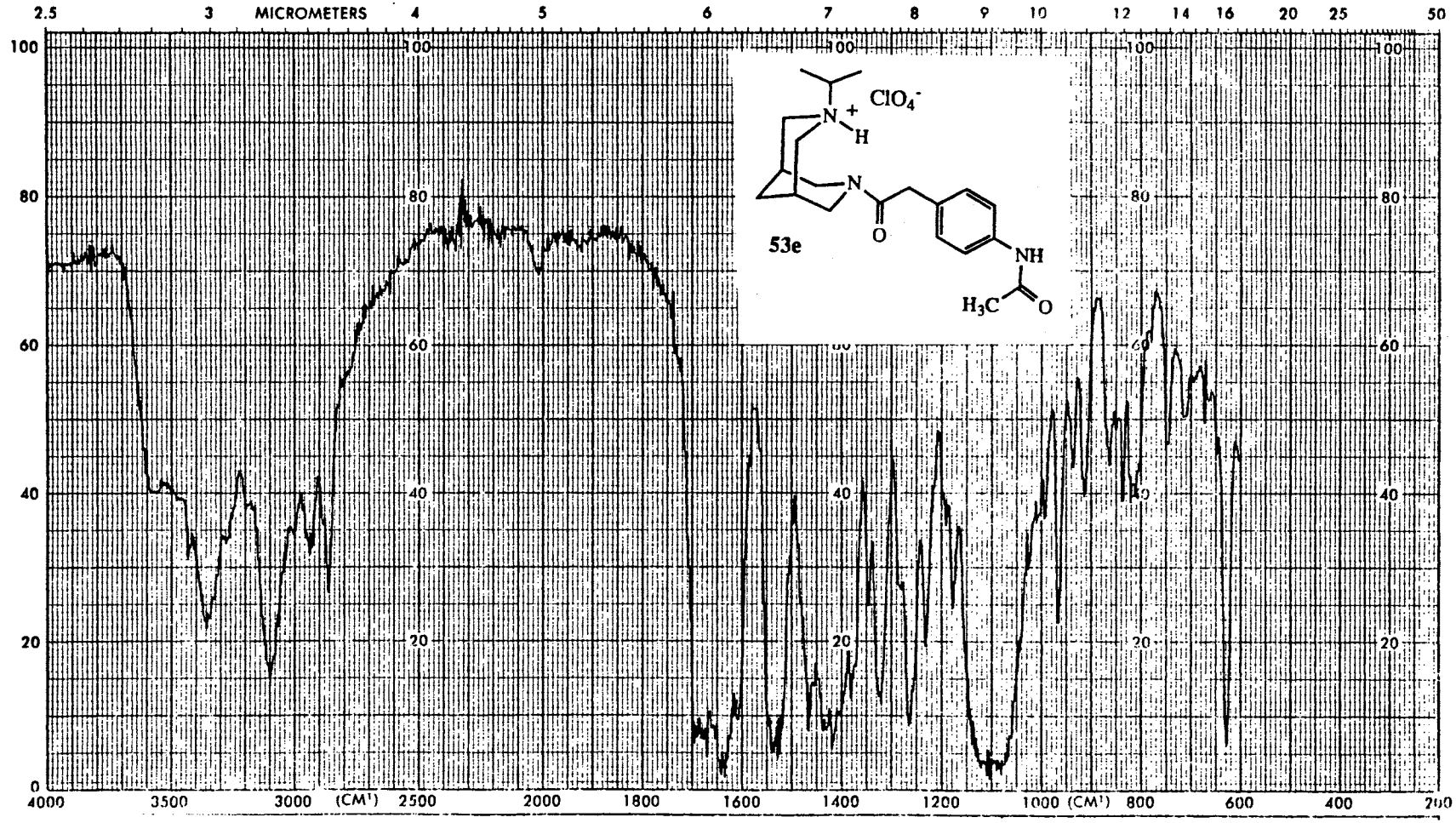
^{13}C NMR Spectrum (-35°C) of **53d**

Plate CI



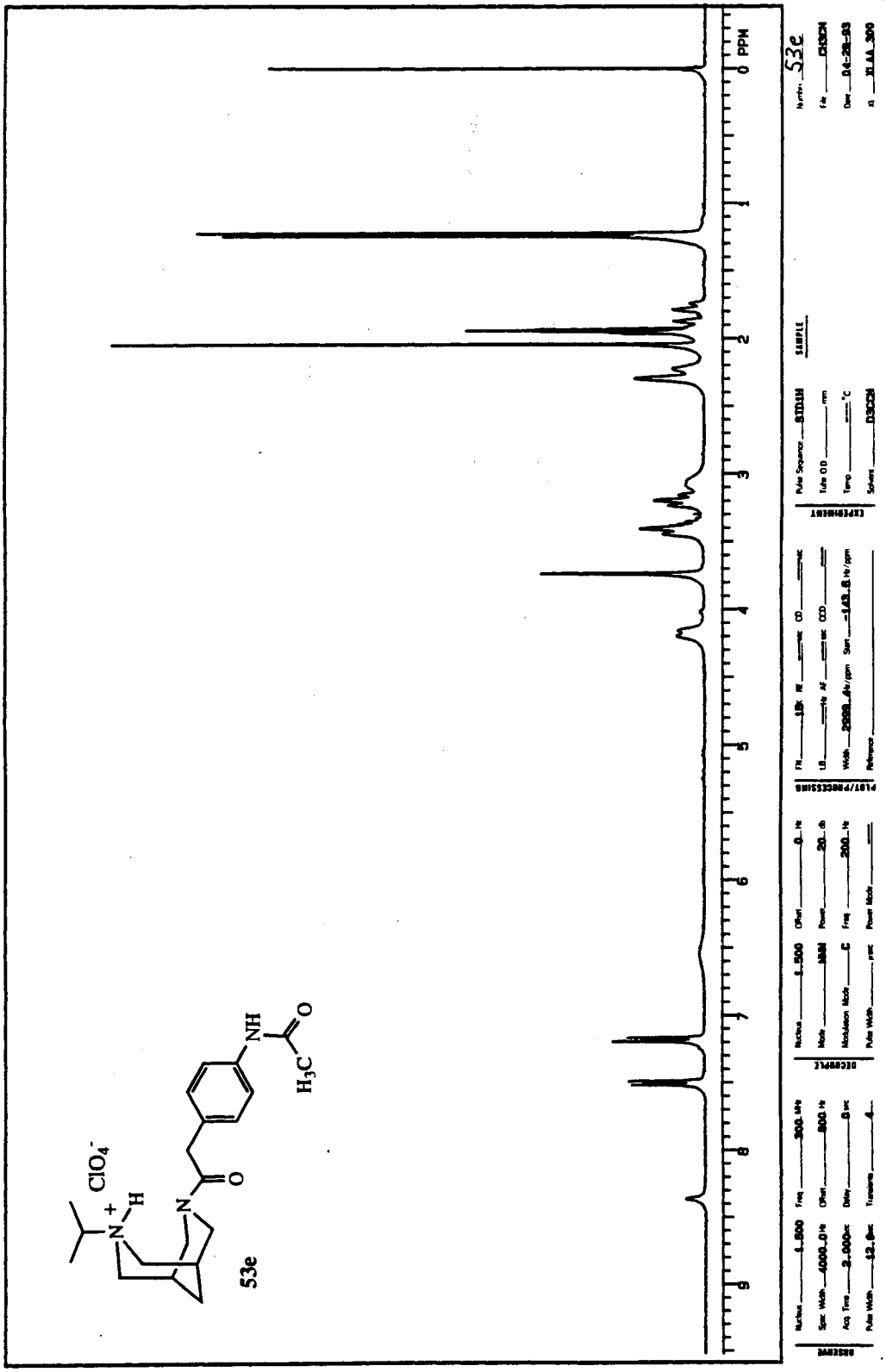
^{13}C NMR Spectrum (60°C) of **53d**

Plate CII



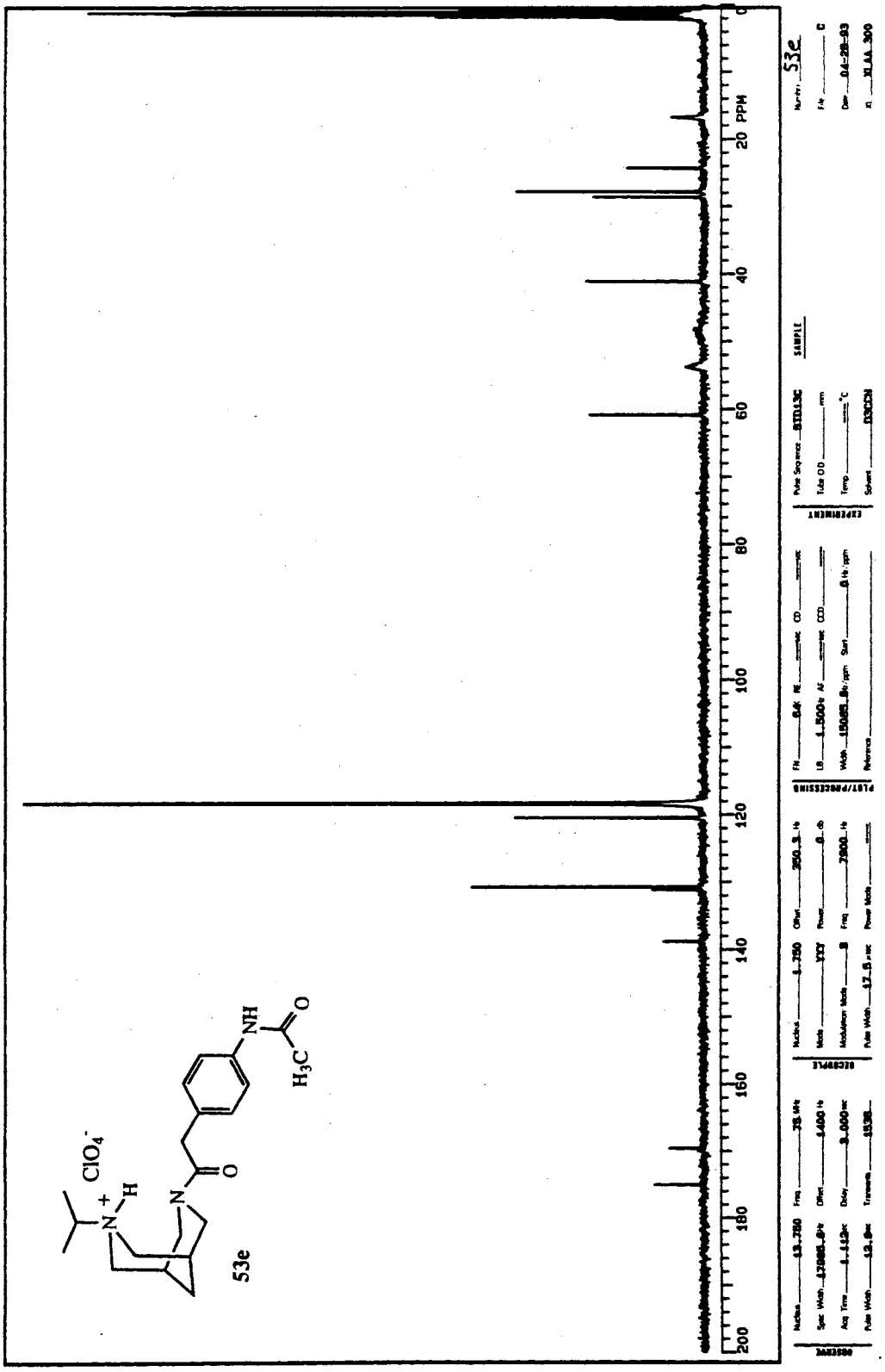
IR Spectrum of **53e**

Plate CIII



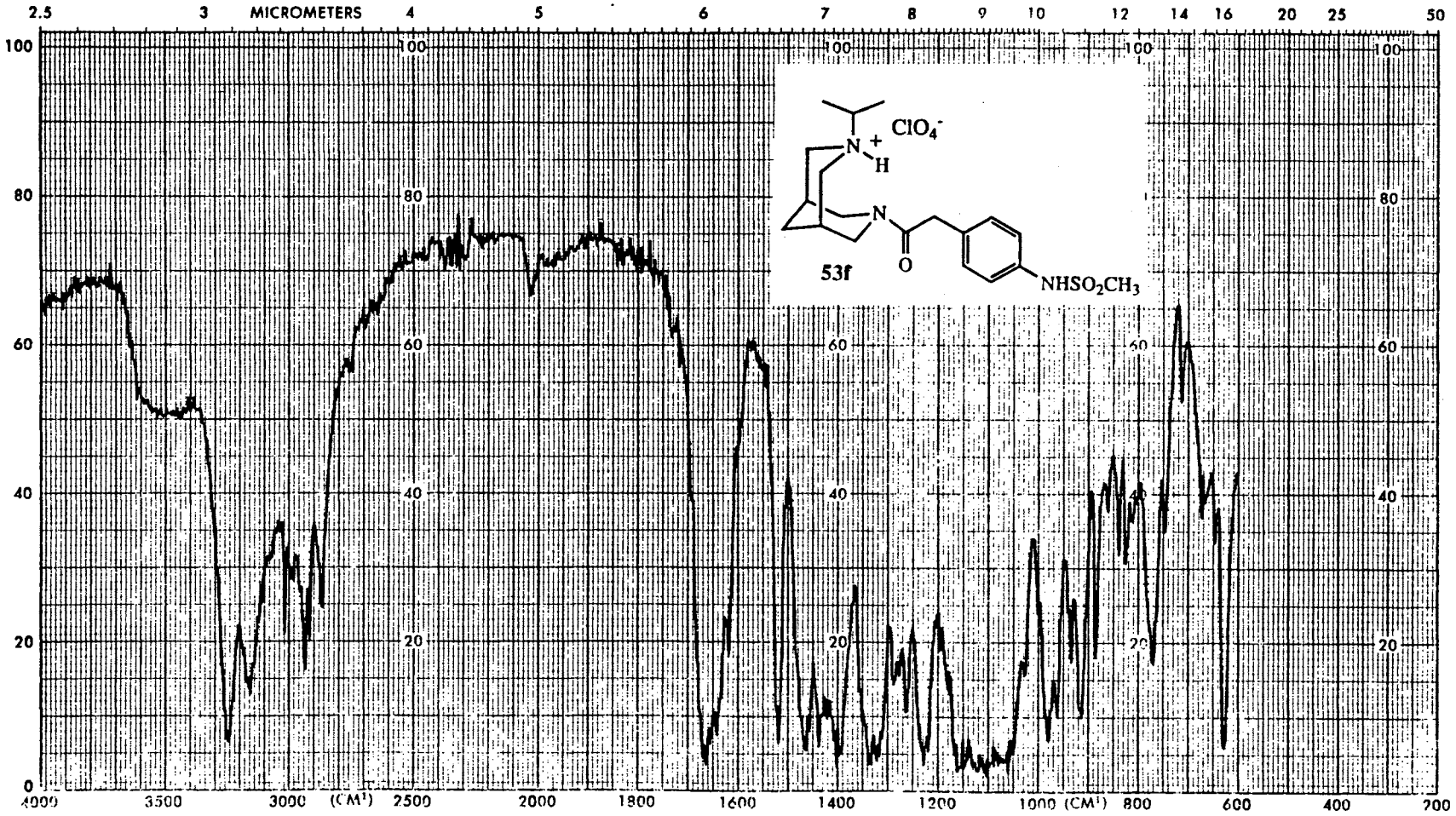
^{1}H NMR Spectrum of 53e

Plate CIV



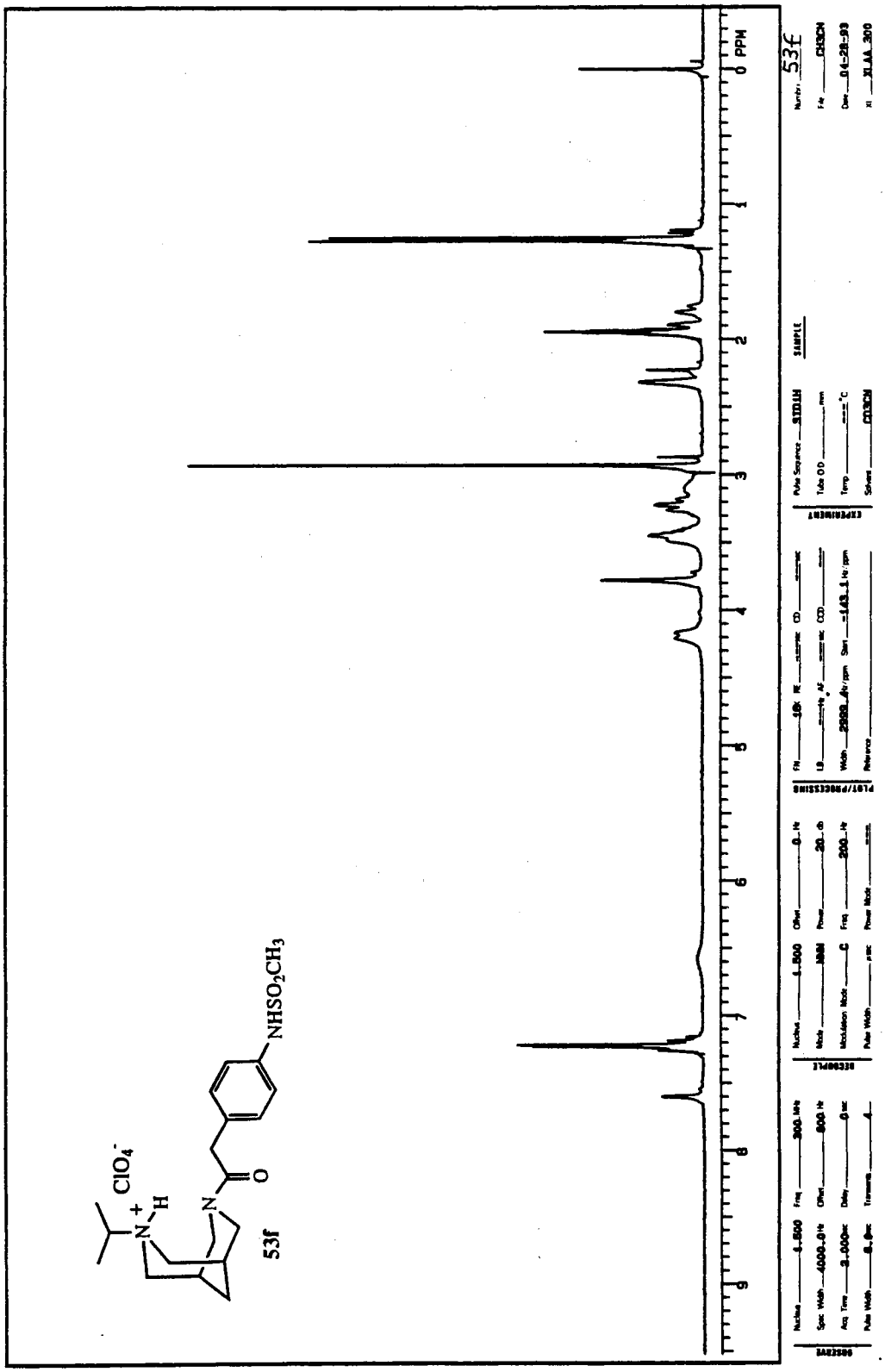
^{13}C NMR Spectrum of **53e**

Plate CV



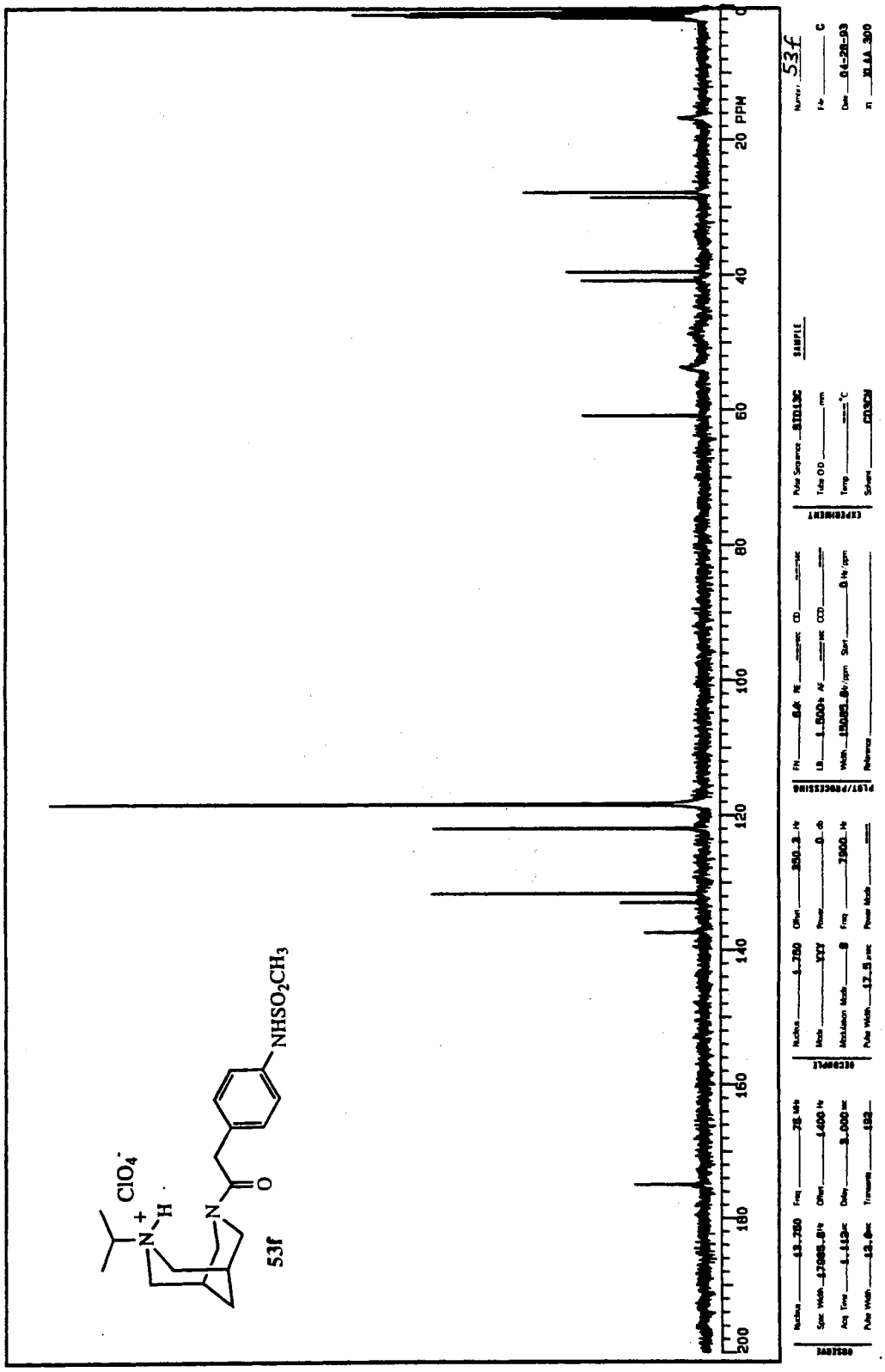
IR Spectrum of **53f**

Plate CVI



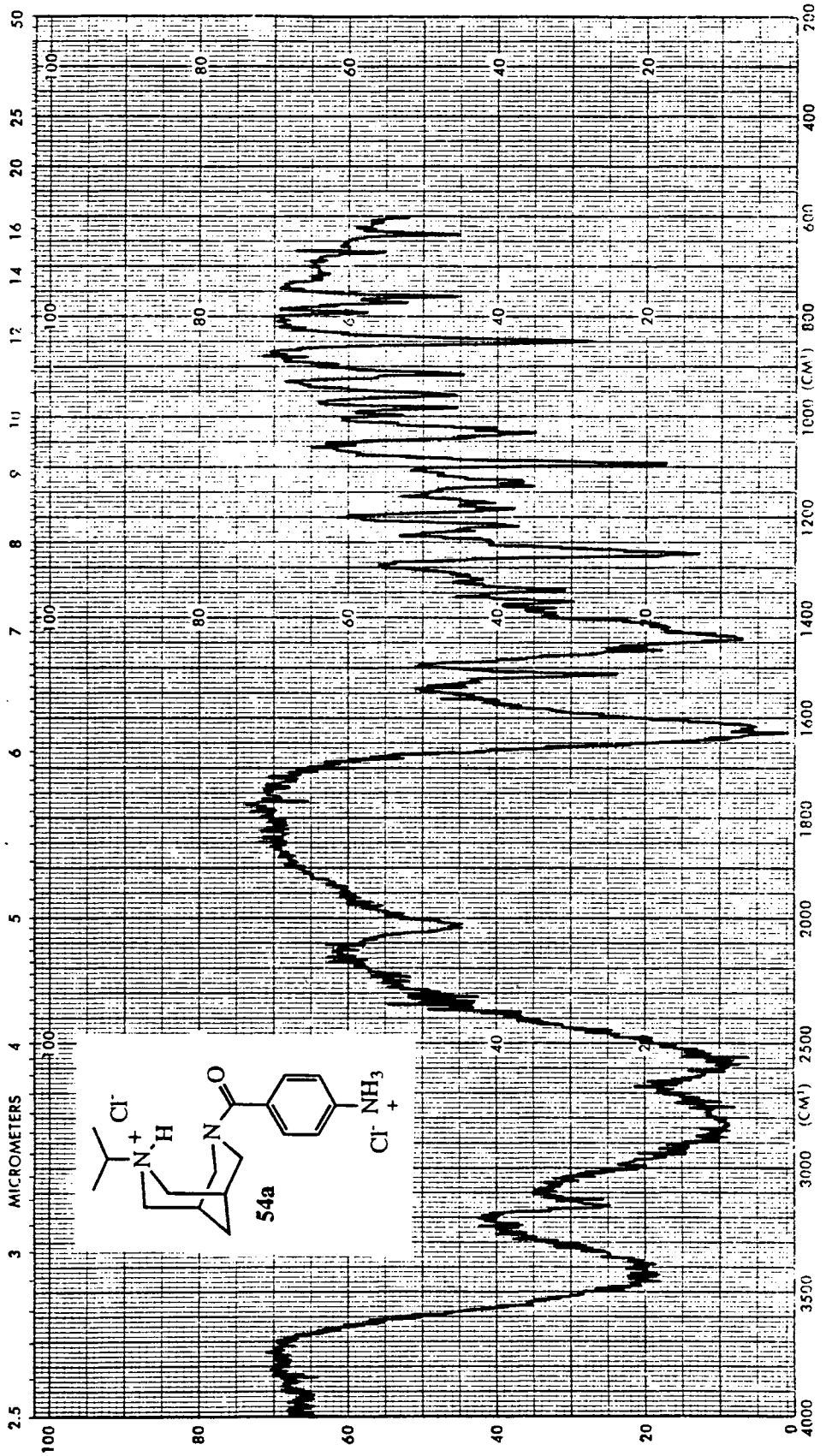
^{1}H NMR Spectrum of 53f

Plate CVII



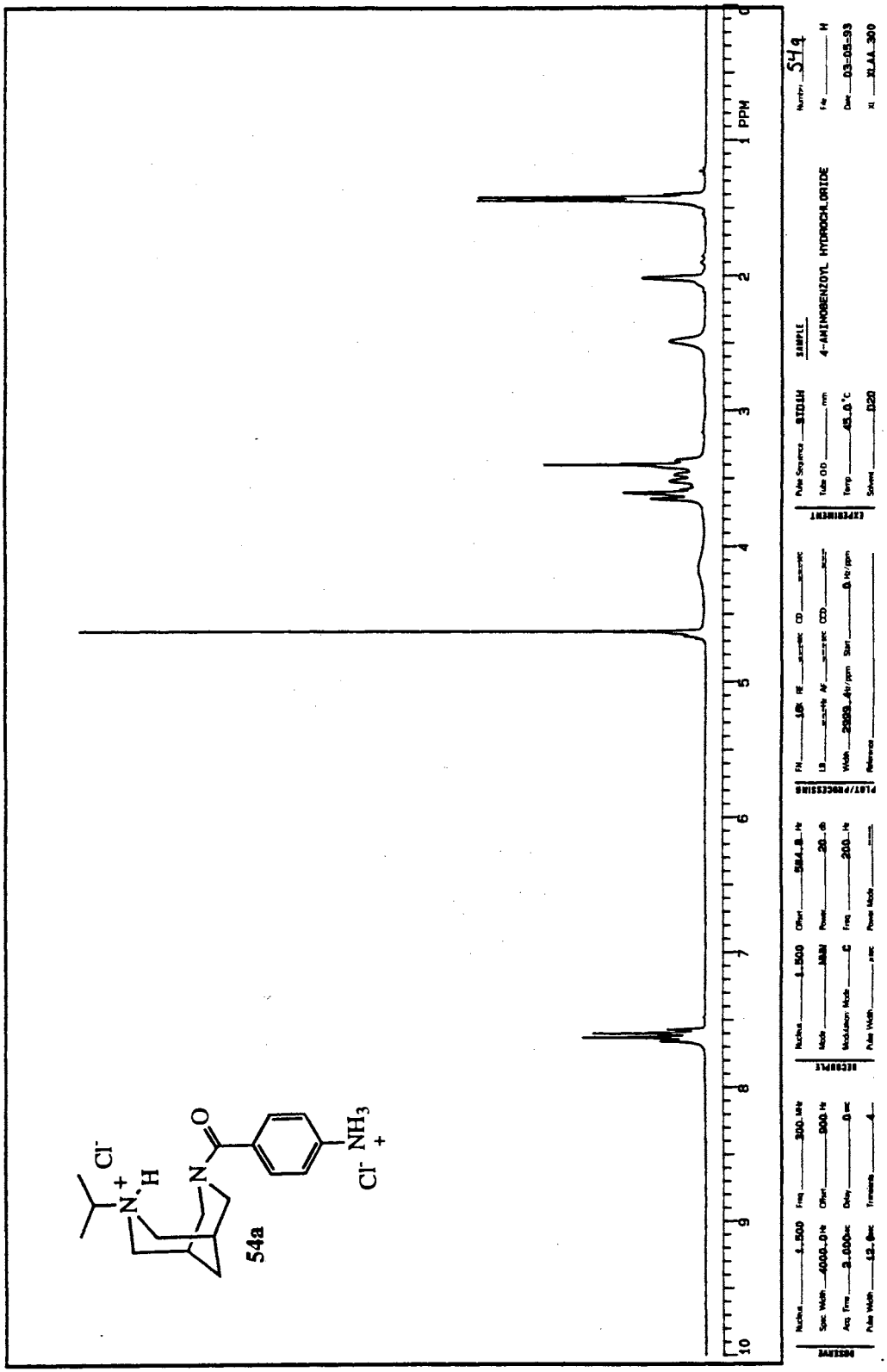
^{13}C NMR Spectrum of **53f**

Plate CVIII



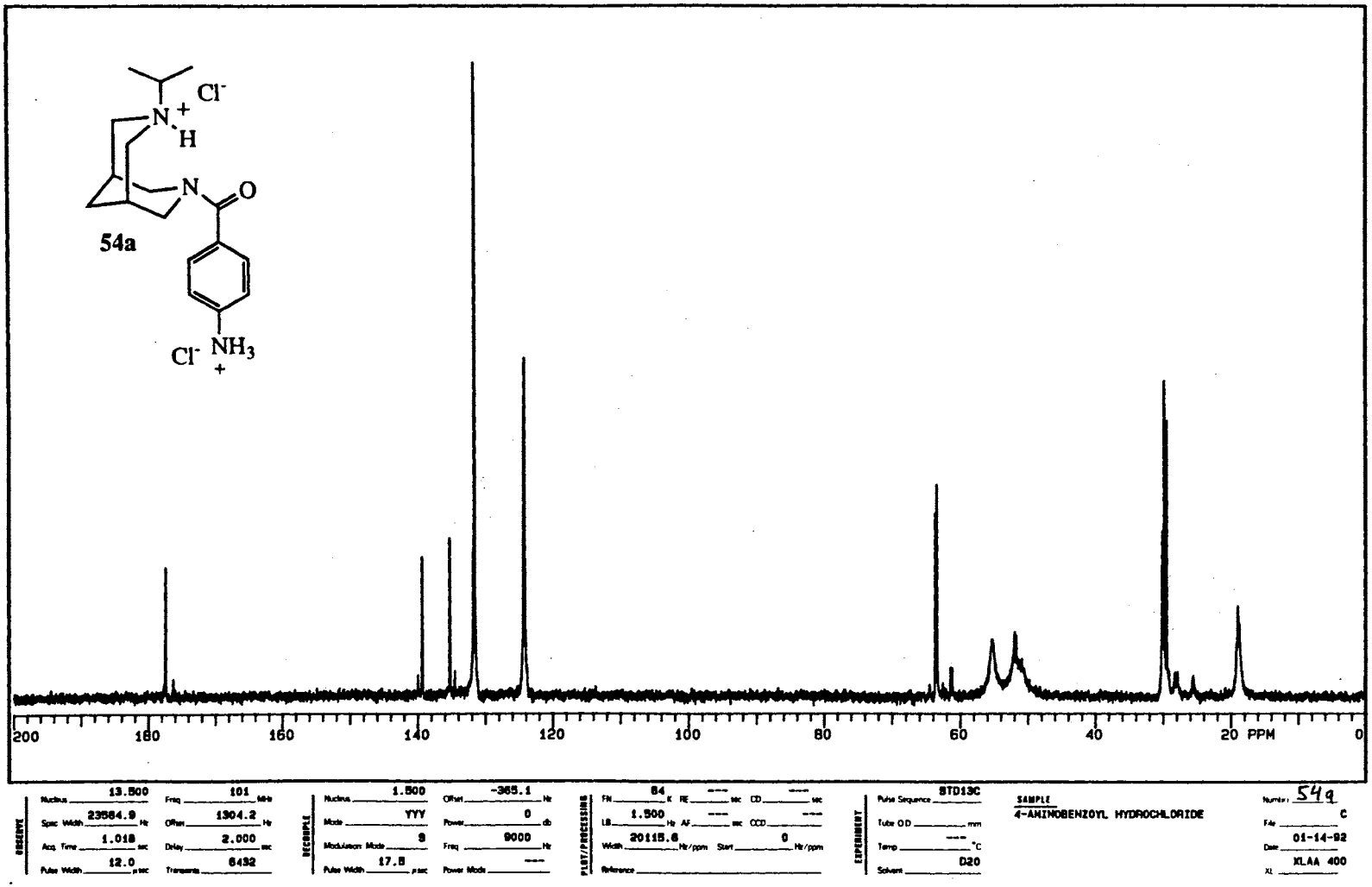
IR Spectrum of **54a**

Plate CIX



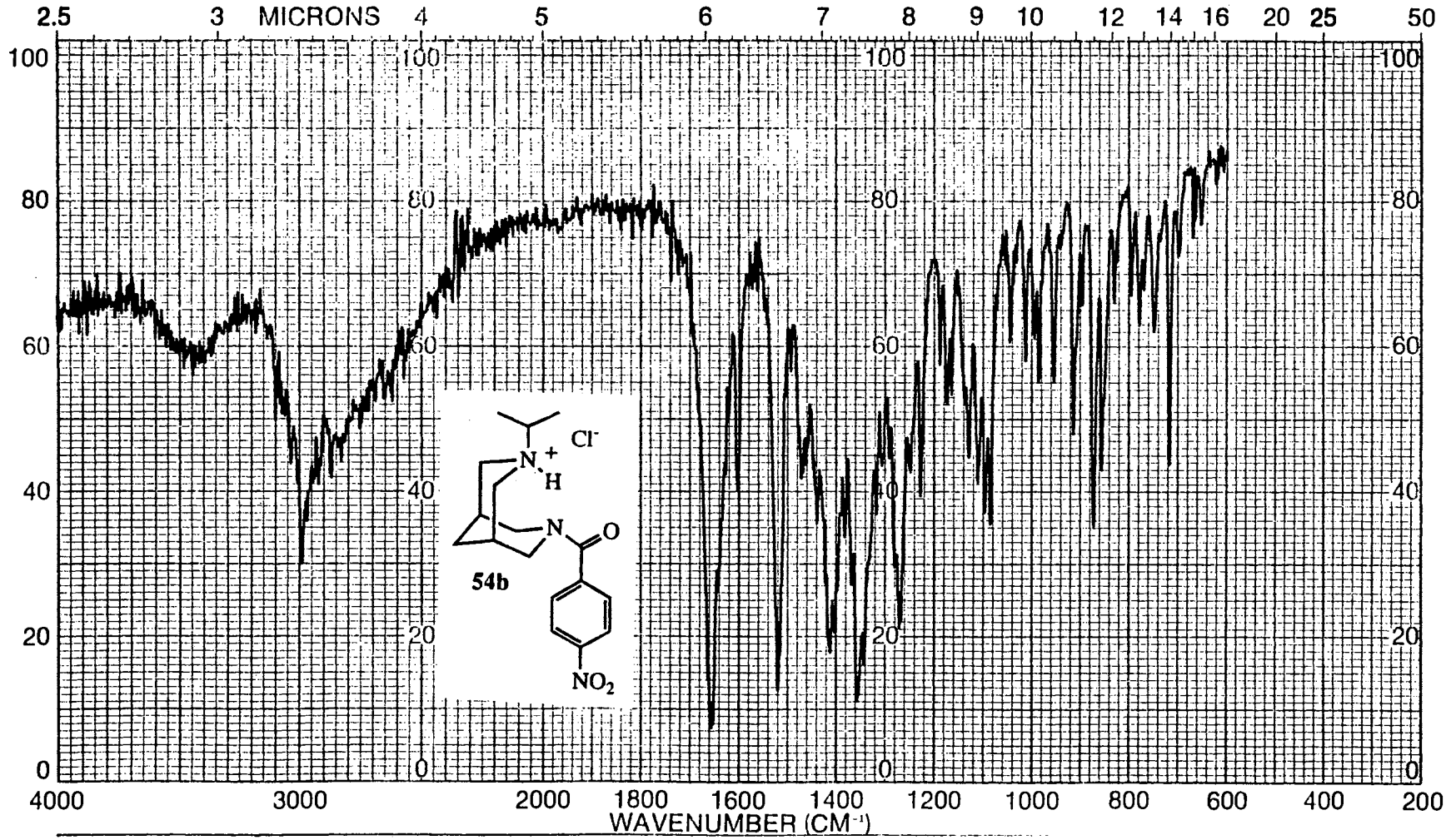
^{1}H NMR Spectrum of **54a**

Plate CX



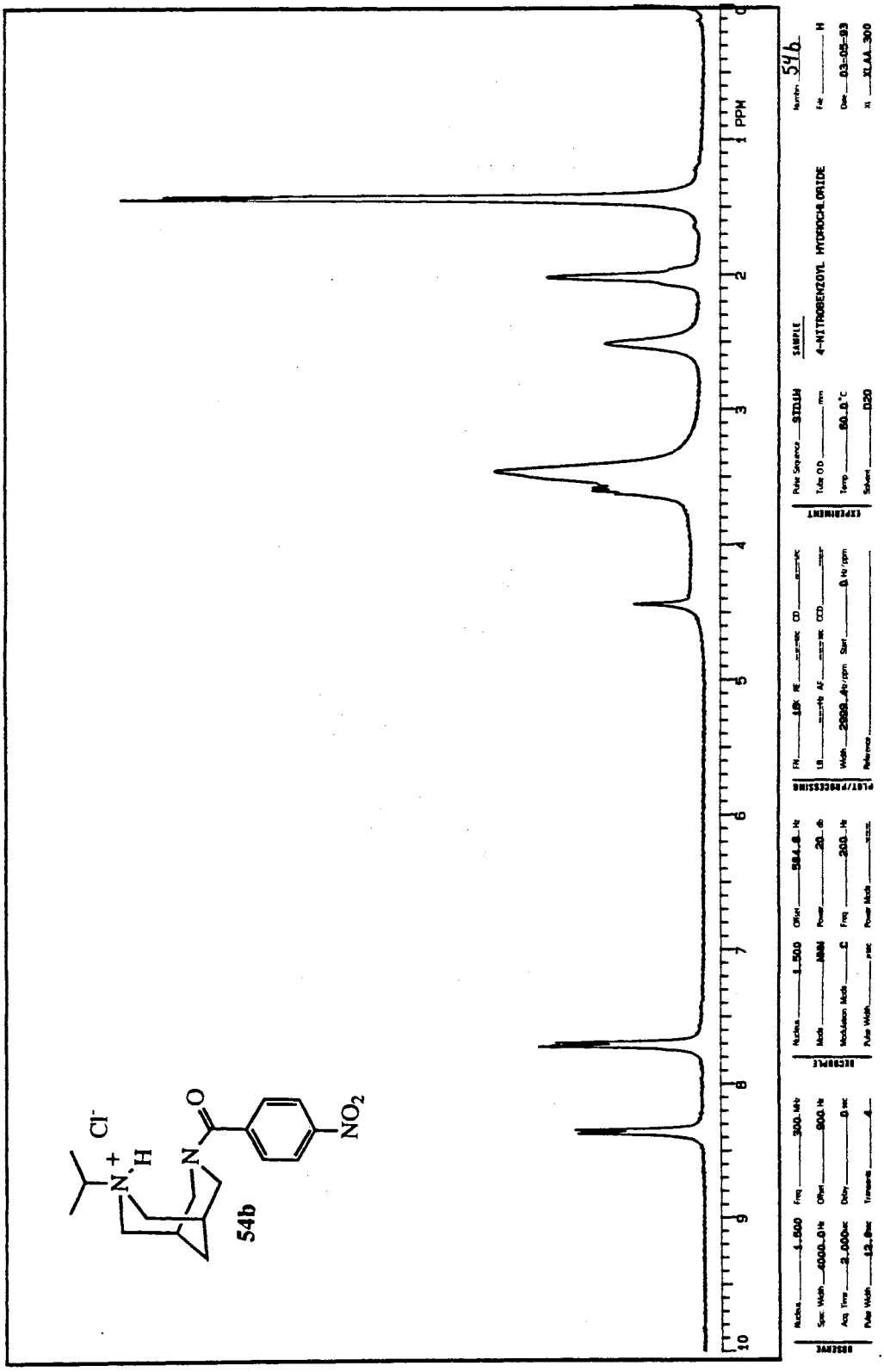
^{13}C NMR Spectrum of **54a**

Plate CXI



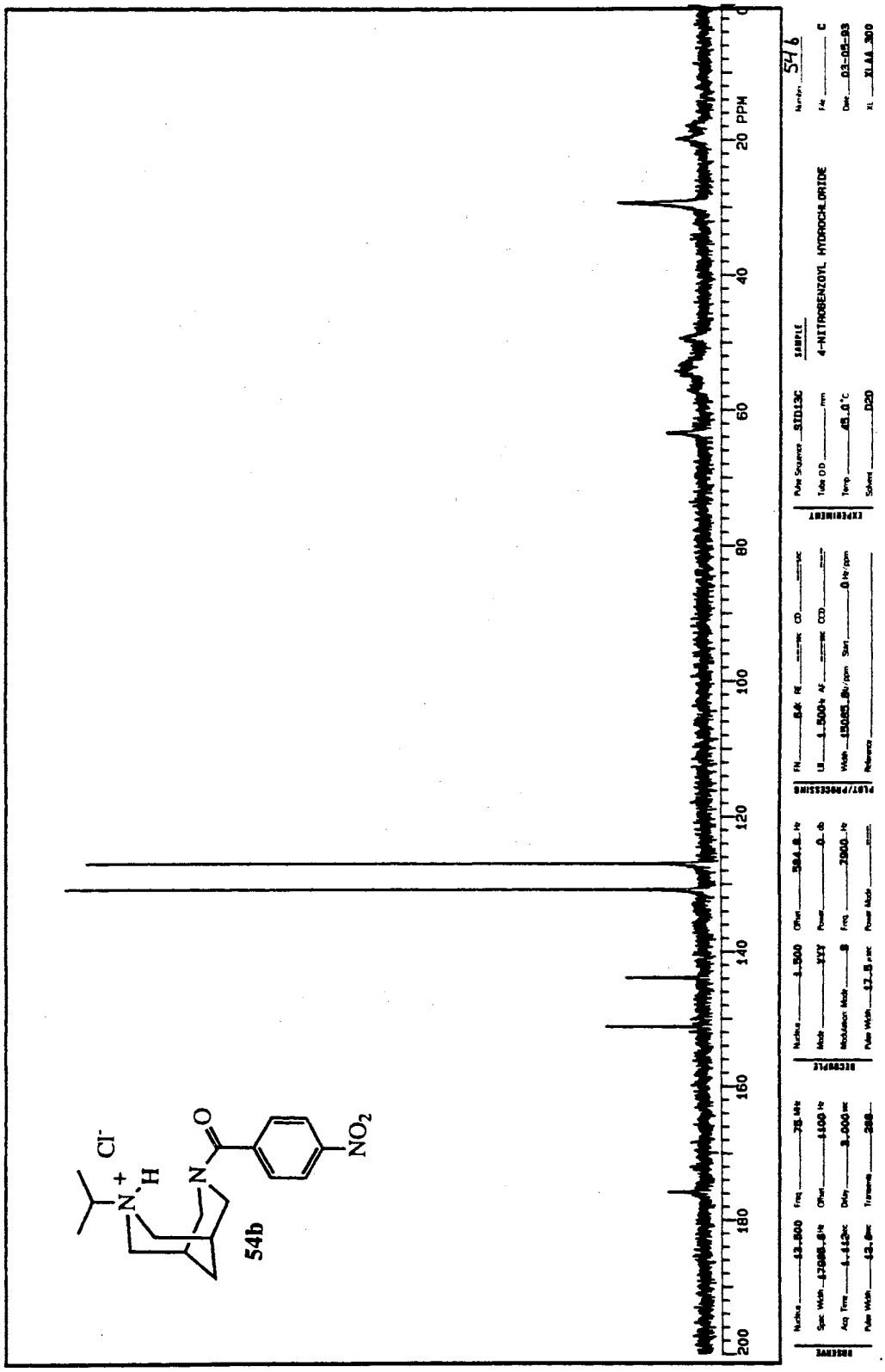
IR Spectrum of 54b

Plate CXII



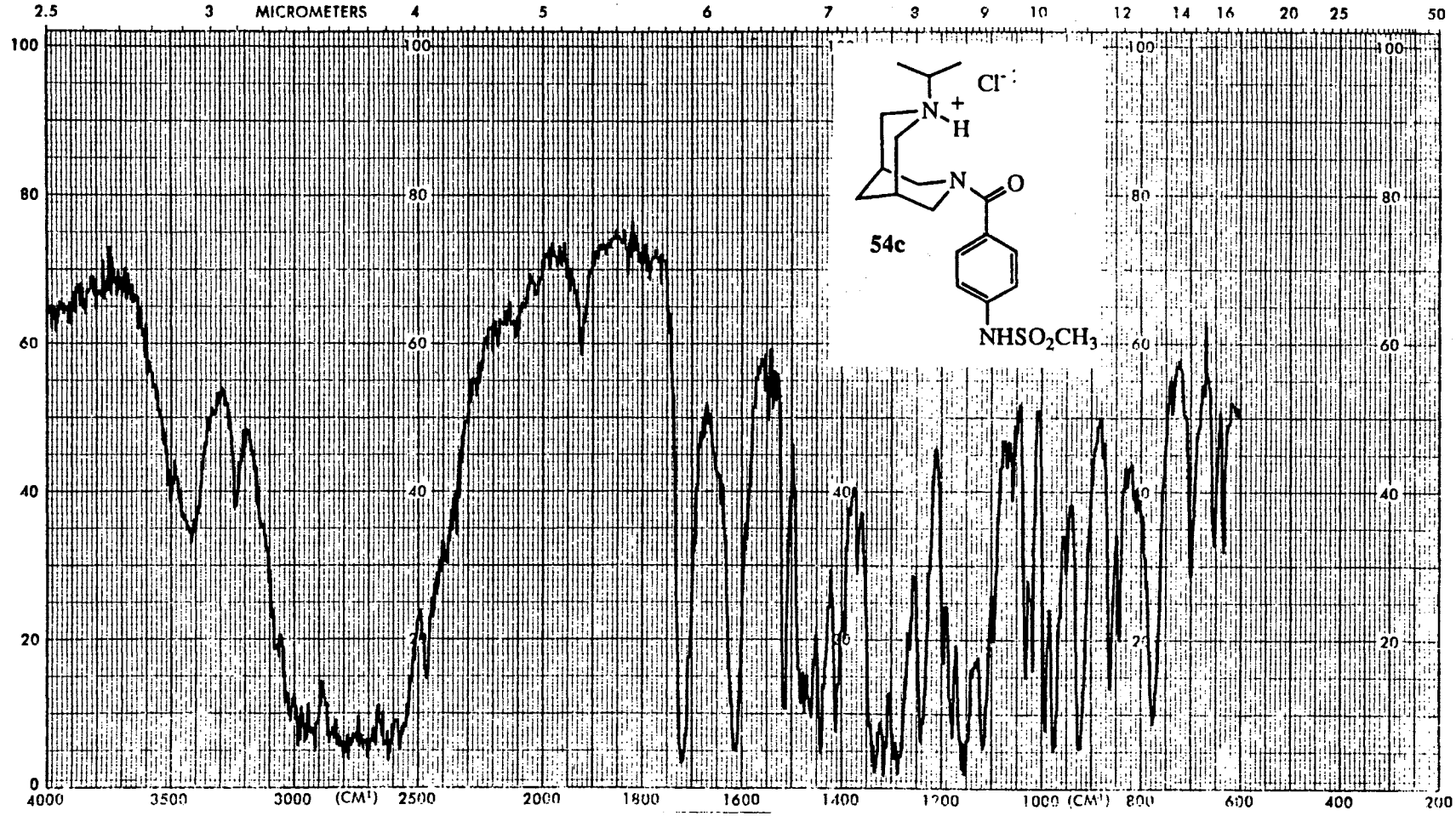
^{1}H NMR Spectrum of **54b**

Plate CXIII



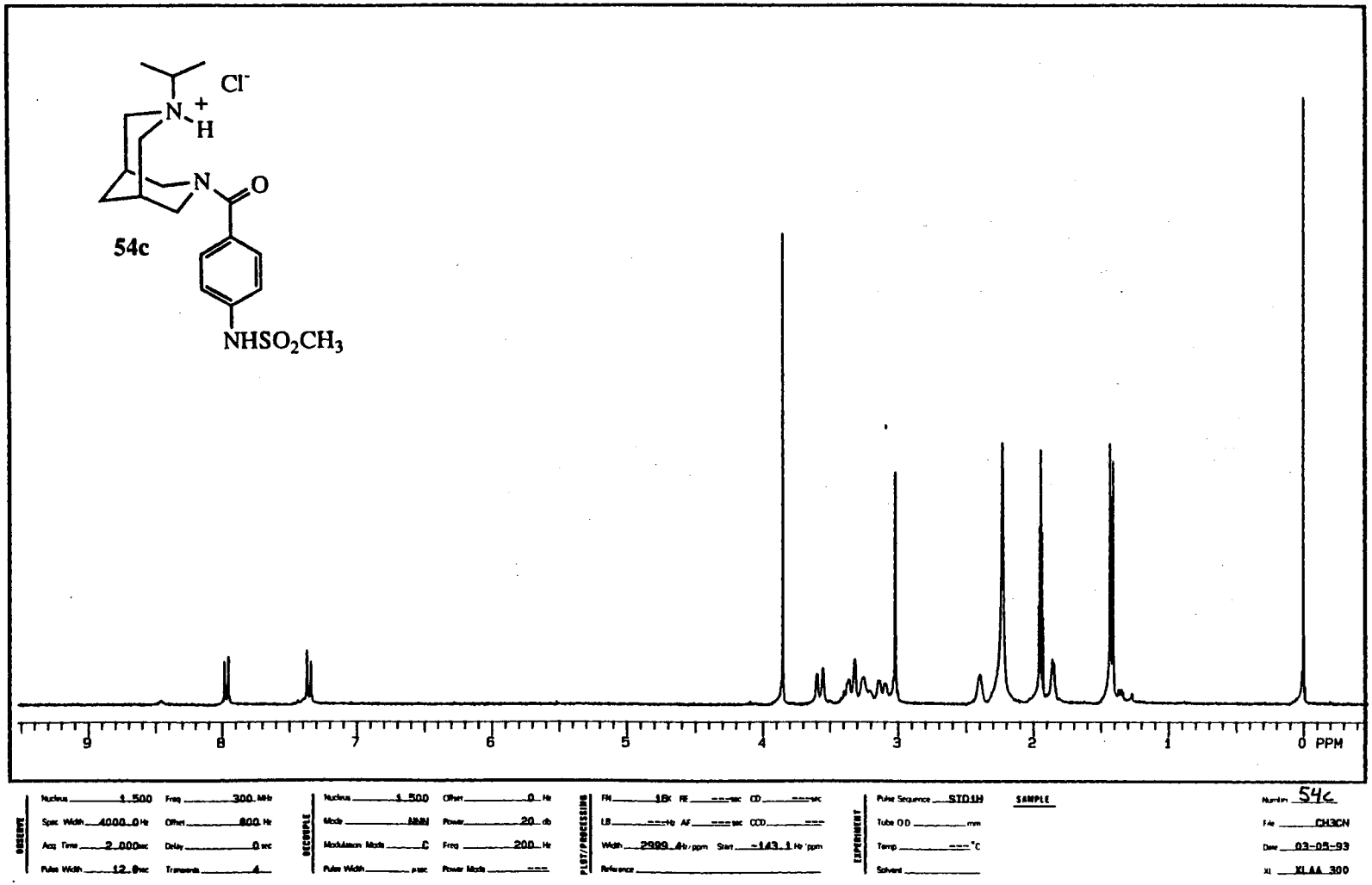
^{13}C NMR Spectrum of **54b**

Plate CXIV



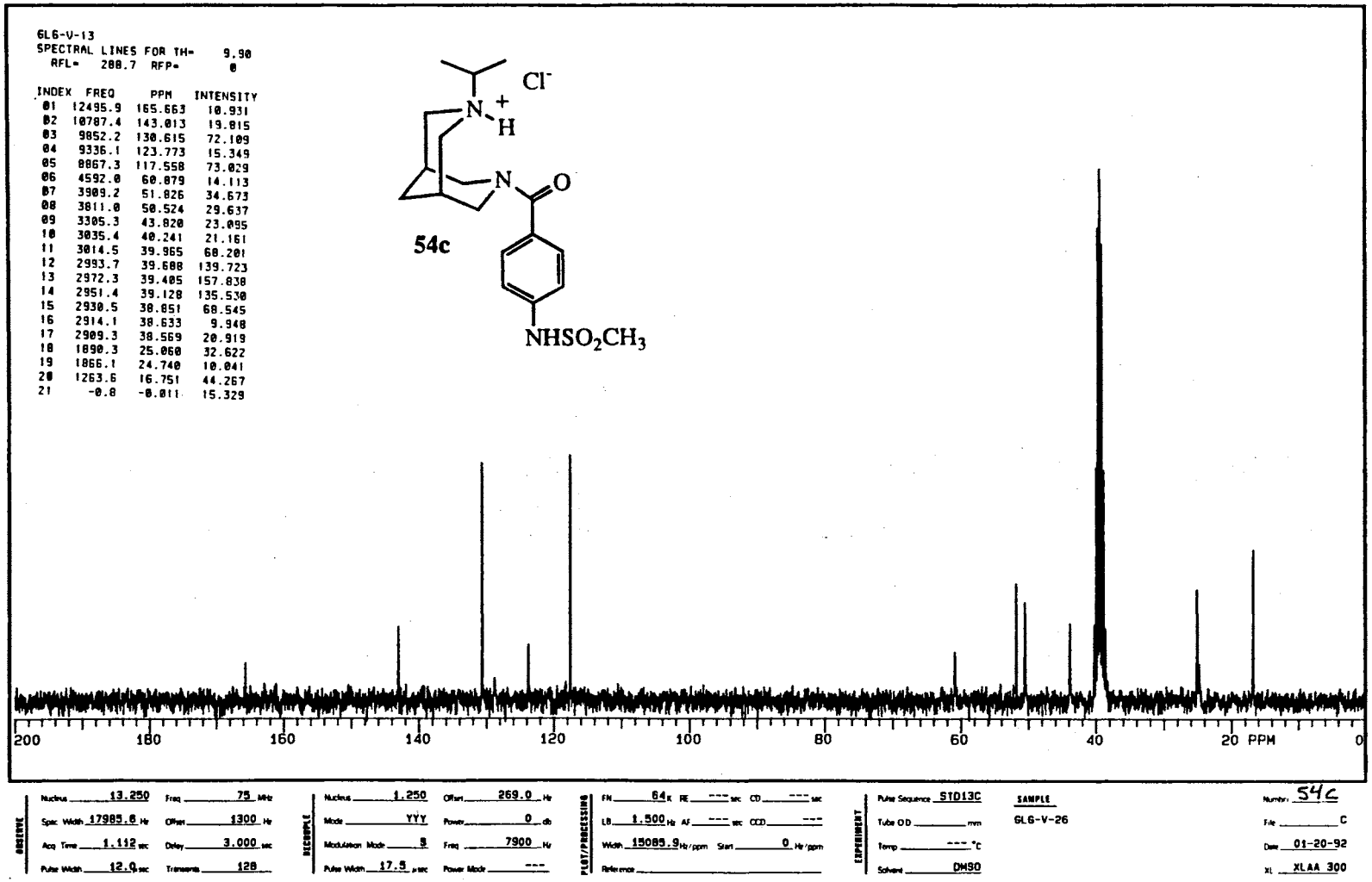
IR Spectrum of **54c**

Plate CXV



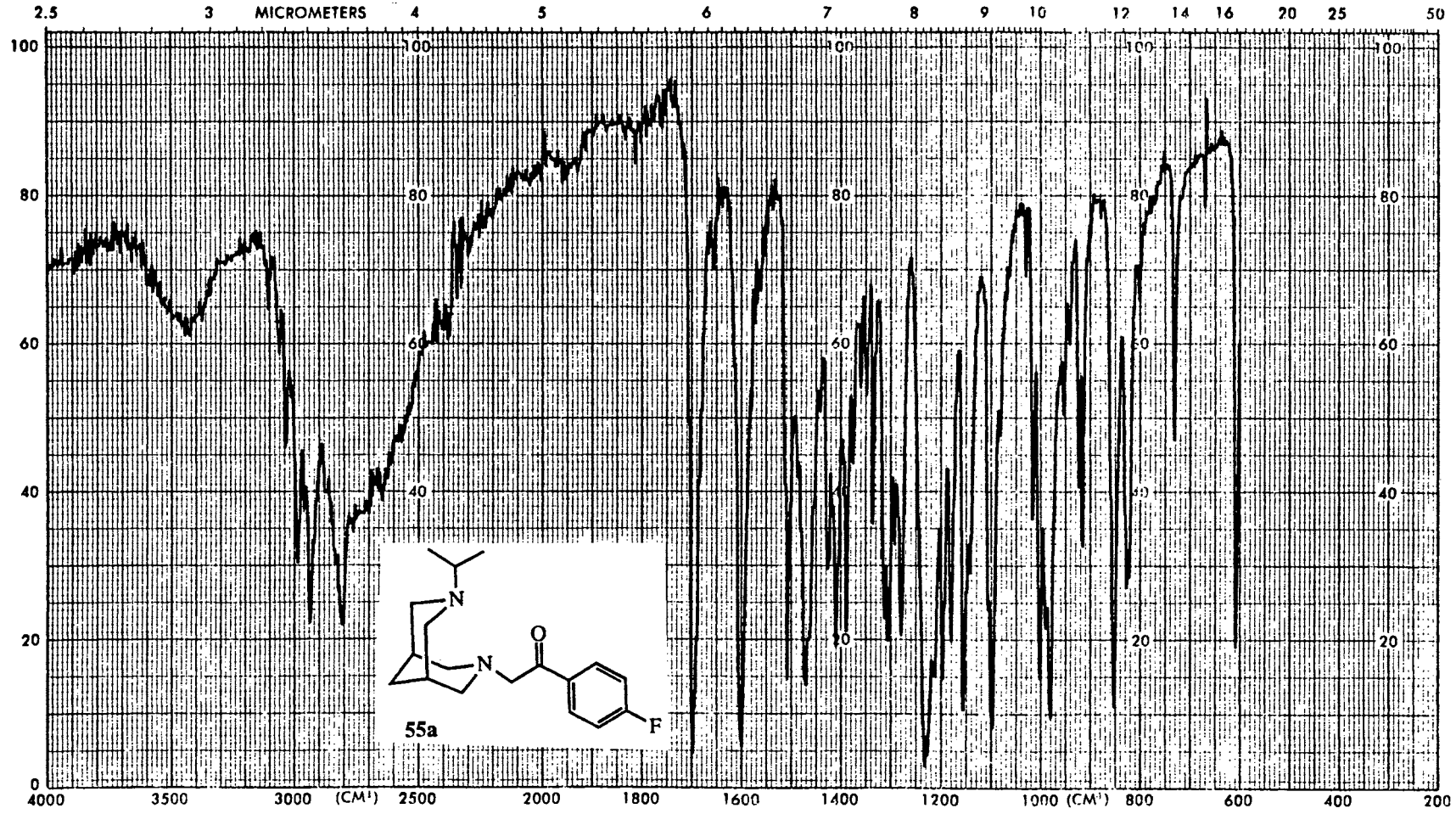
^{1}H NMR Spectrum of **54c**

Plate CXVI



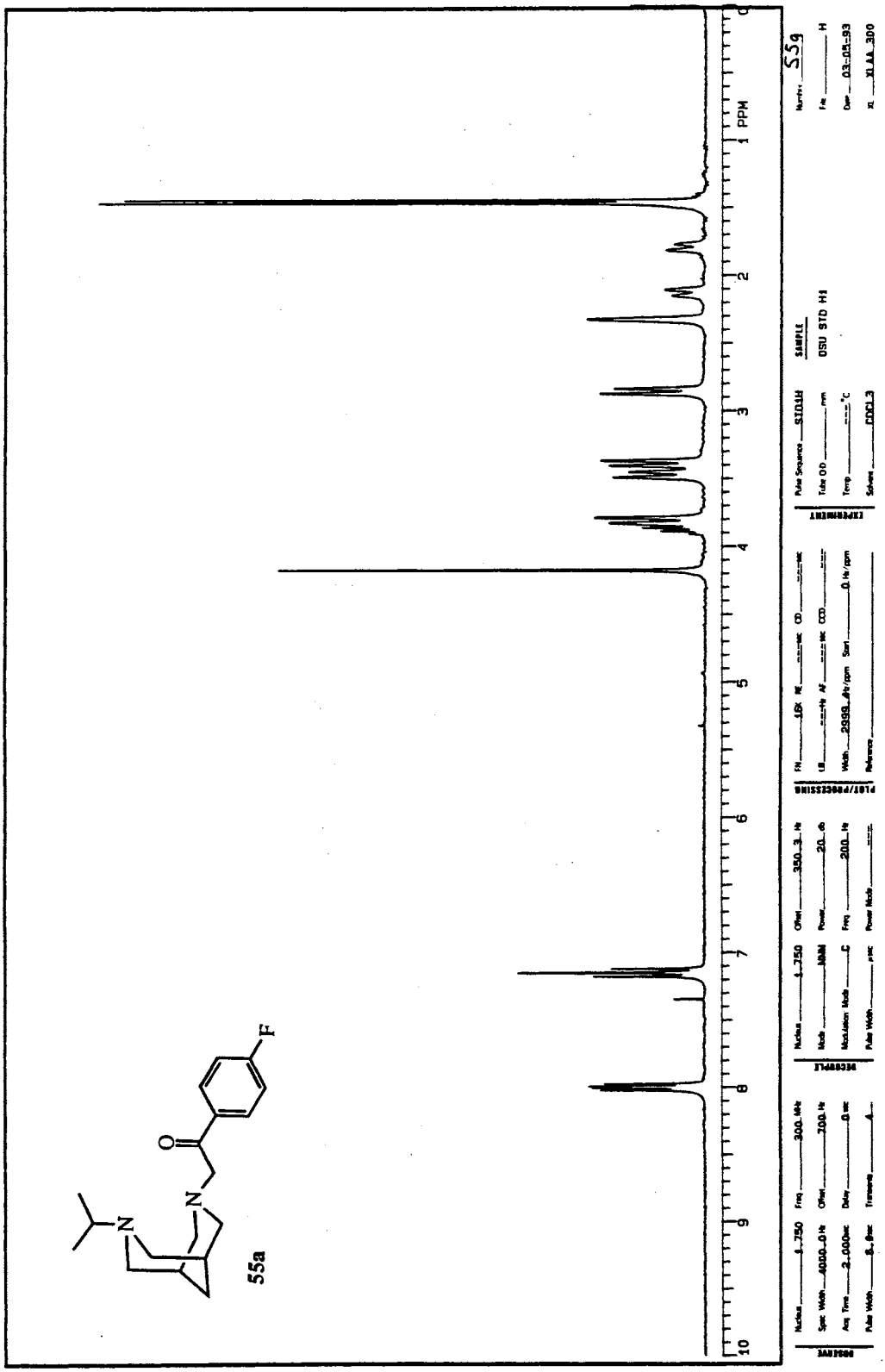
^{13}C NMR Spectrum of **54c**

Plate CXVII



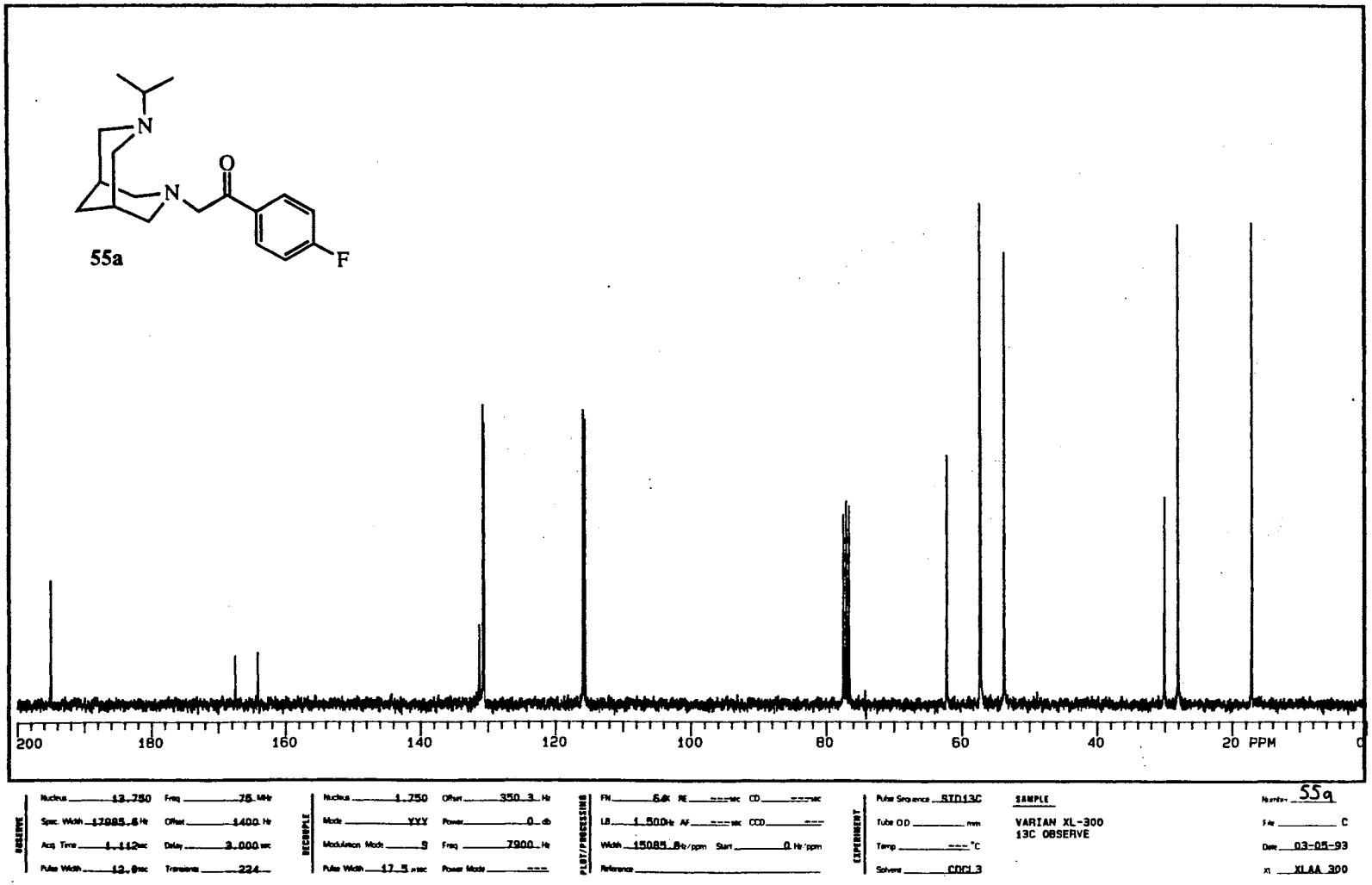
IR Spectrum of **55a**

Plate CXVIII



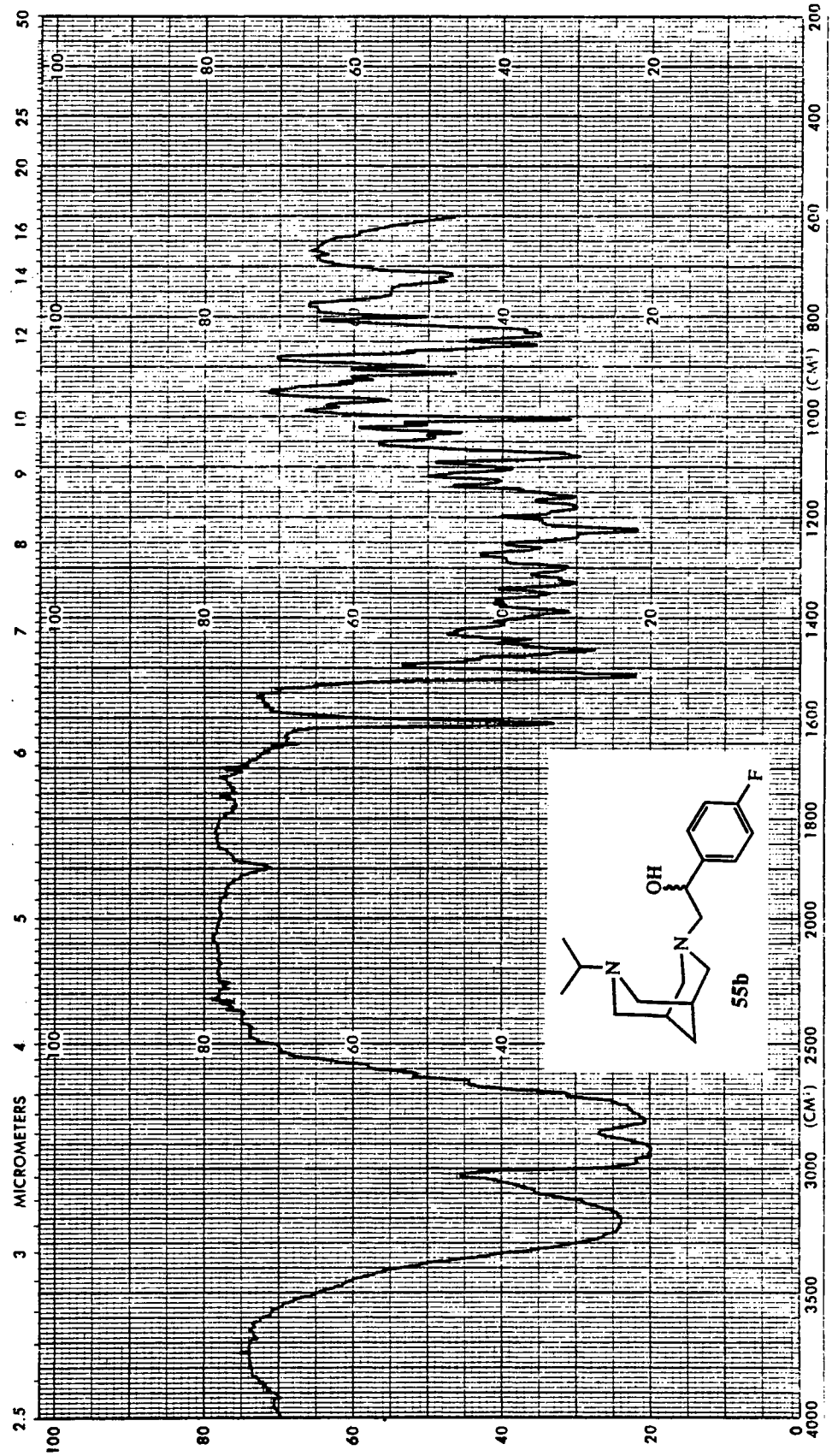
^{1}H NMR Spectrum of **55a**

Plate CXIX



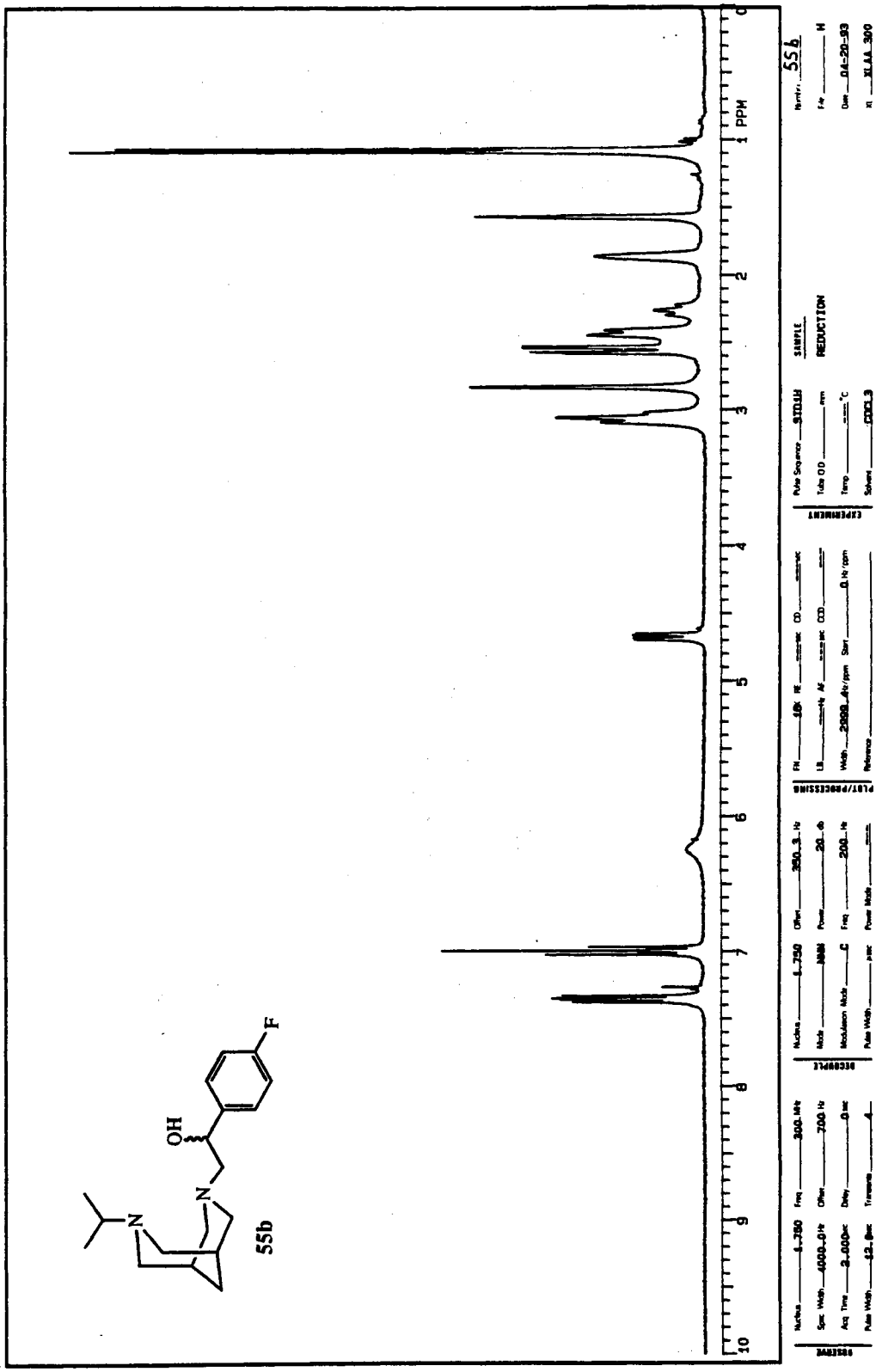
^{13}C NMR Spectrum of **55a**

Plate CXX



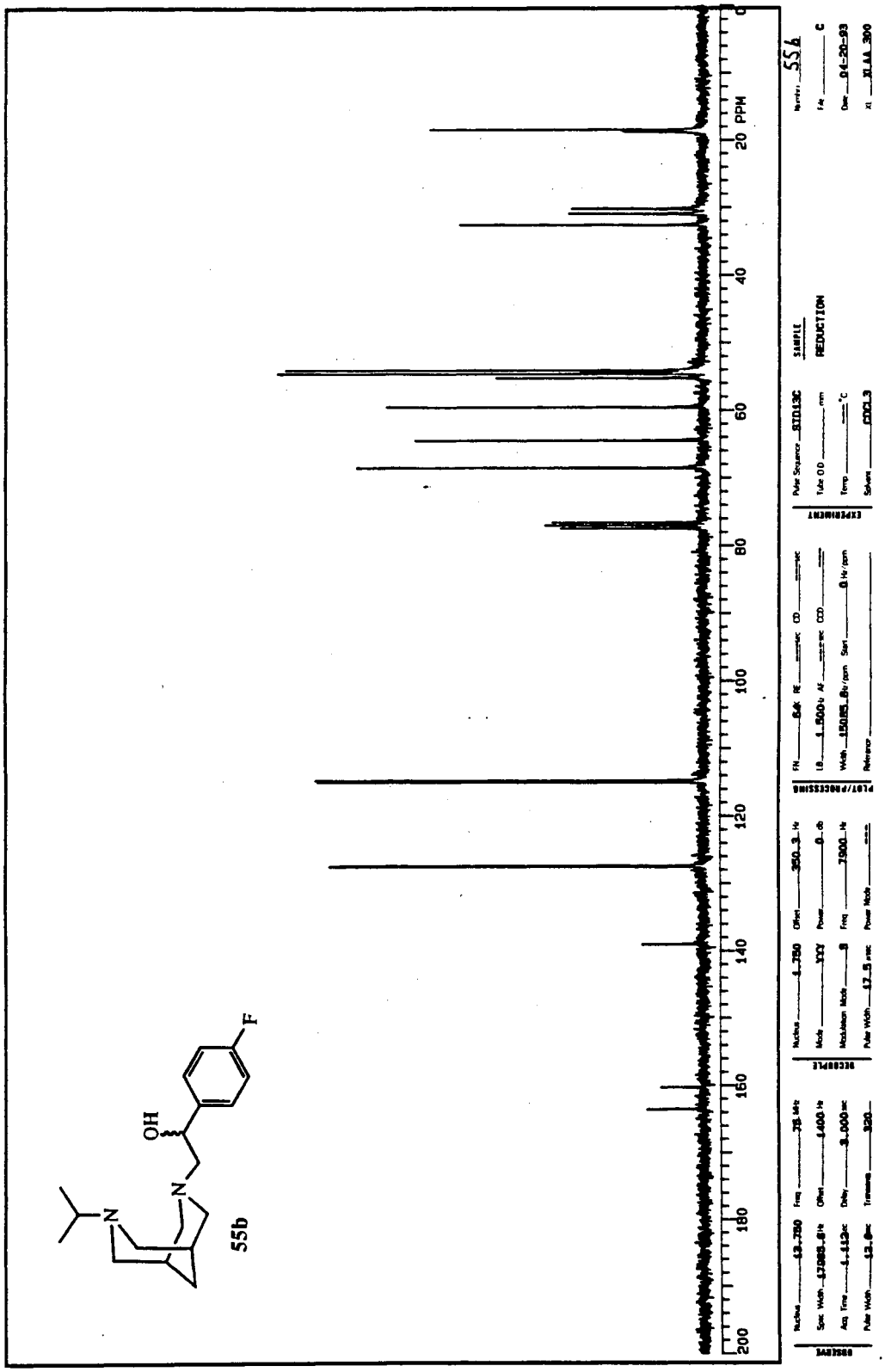
IR Spectrum of **55b**

Plate CXXI



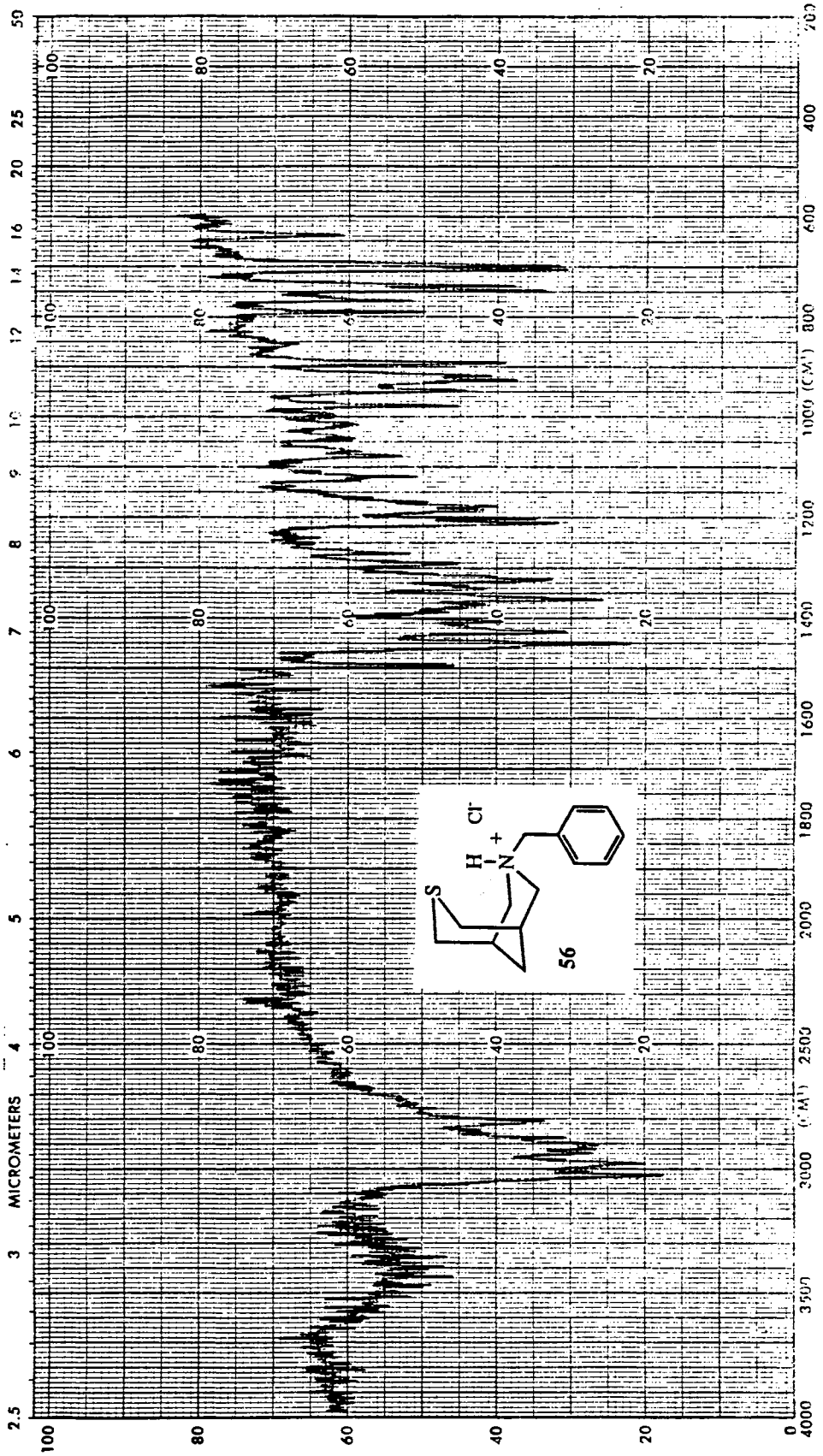
^{1}H NMR Spectrum of **55b**

Plate CXXII



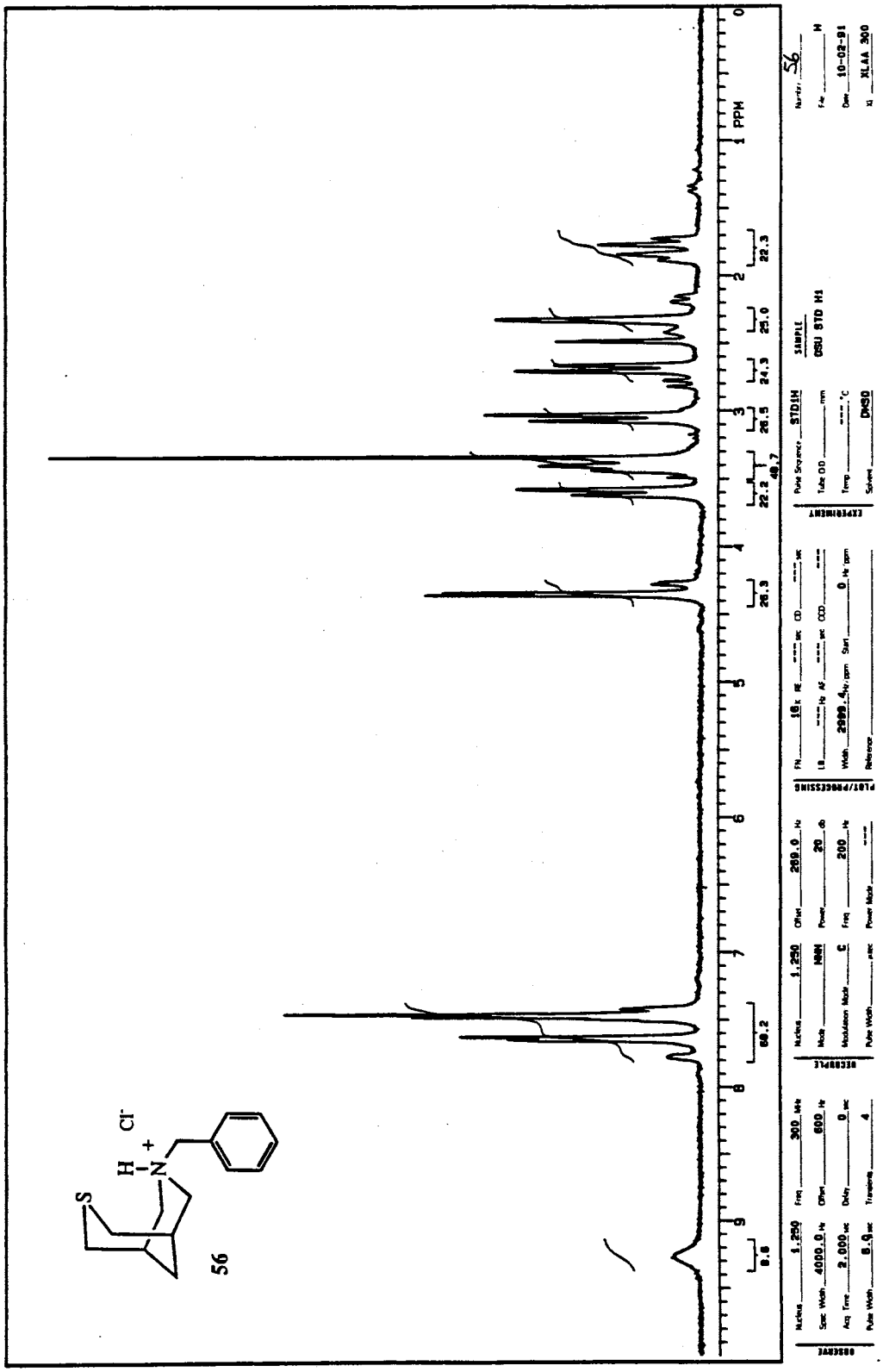
^{13}C NMR Spectrum of **55b**

Plate CXXIII



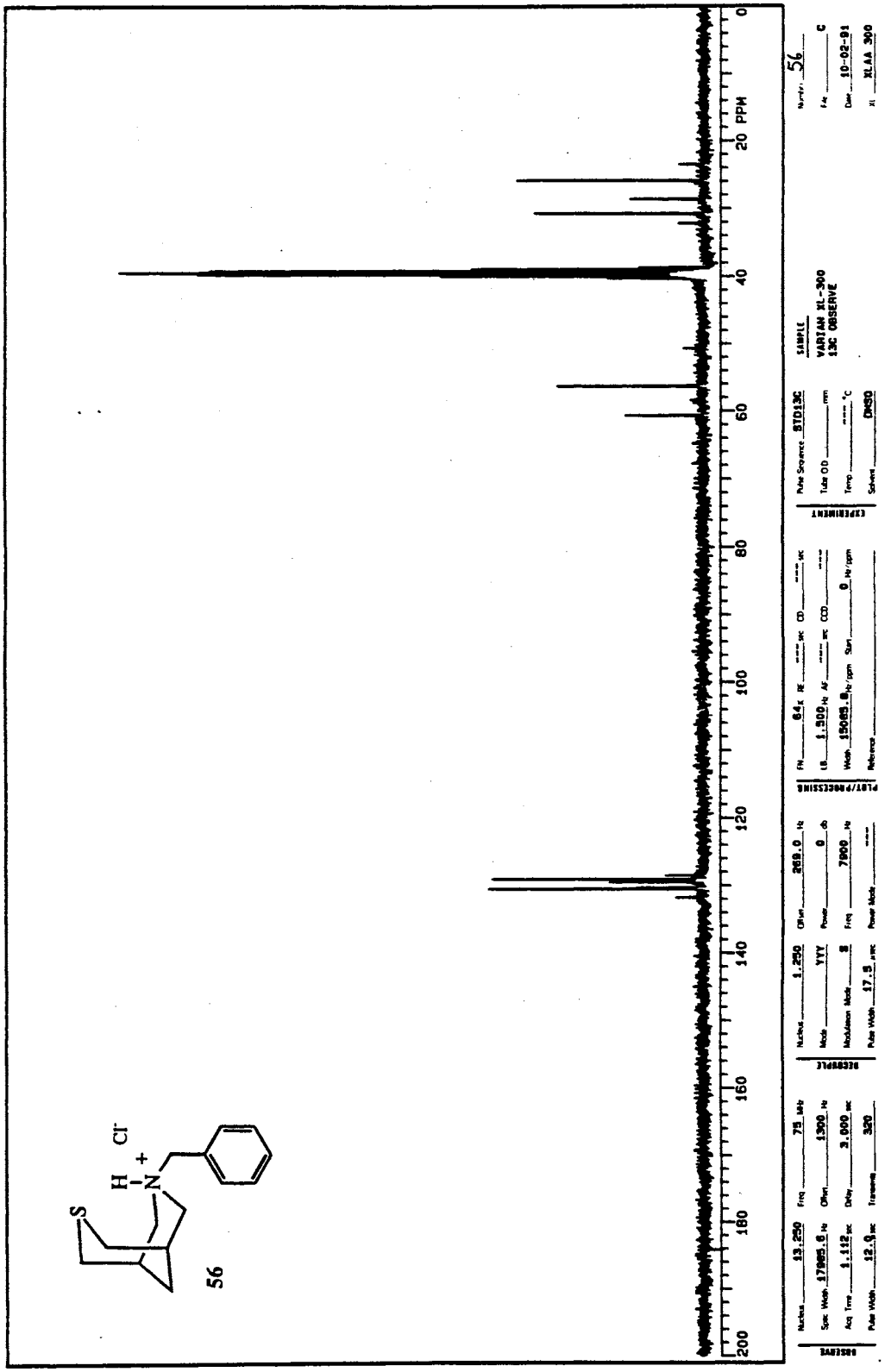
IR Spectrum of 56

Plate CXXIV



^{1}H NMR Spectrum of **56**

Plate CXXV



^{13}C NMR Spectrum of **56**

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VITA

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